DIAGNOSIS OF COELIAC DISEASE IN CHILDREN OF PUNJAB REGION AS PER THE NEW ESPGHAN GUIDELINES

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(MAY 2021)

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ABSTRACT

Introduction: Coeliac disease(CD) sometimes called as sprue or gluten sensitive enteropathy, is an immune mediated inflammatory disorder elicited by the ingestion of gluten and related prolamines in genetically susceptible individuals and characterized by the presence of a combination of gluten dependent clinical manifestations, CD-specific antibodies, HLA DQ2/DQ8 halotypes and enteropathy. Over the last two decades, the understanding of CD has changed from an uncommon enteropathy to a multi organ disease. It is no longer considered a disease of the developed world, its widespread prevalence has been well documented in studies from different developing countries. Prevalence of celiac disease is considered to be around 1% as per the recent studies

Aim of Study: To evaluate triple test serology as a diagnostic criteria for coeliac disease.

Material & Methods: It was a prospective observational study done in our Department of Paediatrics, DMC&H, Ludhiana for one year and six months i.e. from 1st November 2018 to 30th April 2020. All the children in the age group 1 year to 18 years coming to the Paediatric Coeliac clinic of our hospital were included in this study. Diagnosis of coeliac disease was based on revised ESPGHAN (2012) criteria. Triple test and biopsy were done as per guidelines. Out of a total of 56 children that presented with signs and symptoms pertaining to coeliac disease, 44 children met inclusion criteria for this study.

Results: The mean age of the patients included in this study was 7.02 ± 4.07 years. Pain abdomen was the main presenting symptom seen in 90.9% of the patients. In this study, 36 patients were triple test positive. All the cases had a raised Anti-tTG levels, Anti-EMA positivity and were positive for at least 1 celiac-susceptible HLA subtype. A total of 81.8% (36) of the patients were biopsy positive and rest 18.2% (8) were biopsy negative or inconclusive for coeliac disease. Based on these results, specificity for the triple test was 25% and sensitivity was 83.3%, while negative predictive value (NPV) was 25% and positive predictive value (PPV) was 83.3%.

Conclusion: Based on the present study, we concluded that as per the ESPGHAN guidelines, diagnosis of CD can be made with just the use of triple test, without doing the biopsy.

Keywords: Coeliac disease, ESPGHAN guidelines, serological marker, Anti- tTG, anti-EMA, HLA-DQ, diagnosis.

ABBREVIATIONS

ALSPAC	Avon Longitudinal Study of Parents and Children
BSPGHAN	British Society for Paediatric Gastroenterology, Hepatology and Nutrition
CD	Coeliac disease
DGP	Deamidated gliadin peptide
DM	Diabetes mellitus
EMA	endomysial antibodies
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
GC	gluten challenge
GFD.	Gluten free diet
HLA	Human Leukocyte Antigen
IBS	Irritable bowel syndrome
IELs	Intraepithelial lymphocytes
IFD	Iron deficiency anaemia,
IPD	Indoor patient department
mL	Milliliter
OPD	Outdoor patient department
OR	Odd ratio
PCR	Polymrasechain reaction
SBB	small bowel biopsy
SD	Standard deviation
SPSS	Statistical Package for Social Sciences
TLC	Total Leucocyte Count
TT	Triple Test
tTG	Tissue transglutaminase antibodies
U/mL	Units/ml.
ULN	Upper limit of normal
Wt	Weight
Yrs	Years

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INTRODUCTION

Coeliac disease (CD) is an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals and characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies. The consumption of gluten containing foods is necessary for CD to develop. [(1)] Gluten is the viscoelastic protein that remains after washing dough and is composed of alcohol-soluble gliadins and alcohol-insoluble glutenins. Epidemiologic and prospective observational studies implicate a range of environmental factors that impact disease development. [(2)]

Although gluten interacts with and damages the small intestinal mucosa, the primary host defect requires trigger. [(3)] Some hypothesize that an enzyme deficiency leads to incomplete gluten digestion in patients with coeliac disease. As a result of this deficiency, a toxic peptide accumulates; it may then damage the susceptible small intestinal mucosa. Others believe that abnormal glycosylation of apical membrane glycoproteins on the enterocyte facilitates a lectin-like interaction between gluten and small intestinal absorptive cells. [(3,4)] Although (proteins largely derived from plants with a specificity for certain sugar residues) may bind to the damaged small intestinal mucosa of coeliac disease, there is no published evidence that such differences persist with mucosal healing and treatment with a gluten-free diet.

While environmental factors are important for CD development a notable feature of CD is its high heritability and strong Human Leukocyte Antigen (HLA) association. This strong genetic association reflects the central role of CD4+ T cells as the HLA molecules associated with CD bind specific gluten peptides that activate T cells. The contribution of non-HLA genes to CD risk susceptibility is much less strong (OR < 1.5) than the HLA-associated haplotypes (OR >5) but collectively are significant. More than 70 candidate genes in over 40 non-HLA loci have been implicated in CD heritability. [(5)]

The proximal small intestine is the major site of disease. Increased intraepithelial lymphocytosis, with or without concomitant villous atrophy, is the characteristic histological finding. The events that culminate in the histological changes of CD are incompletely understood. Gluten T cell epitopes cluster in regions of high proline making them resistant to the effect of gastrointestinal proteases.[6] These peptides may pass across the epithelium via transcellular [7, 8] and paracellular (receptor or antibody mediated) pathways.[9] Increased epithelial permeability, a feature of active CD, may be mediated by a direct effect of gliadin acting via the chemokine receptor CXCR3 in intestinal epithelial cells on tight junctions. [9] Dendritic cells are presumed to play a major role in presentation of gluten peptides to CD4+ T cells, however little is known about their identity, where this presentation occurs, and the extent to which this role is undertaken by gluten-specific B cells. [10]

The diagnosis of CD can be made by

Clinical symptoms

Serum antibodies

HLA association

Histology

A number of asymptomatic children will be diagnosed with CD following CD can present with wide range of symptoms and can largely be divided into intestinal and extra-intestinal features. Intestinal features include diarrhea, abdominal pain, bloating, weight loss and constipation. Extra-intestinal features include unexplained iron deficiency anemia, short stature, faltering growth, constipation, liver disease, arthropathy, ulcers, muscle weakness, delayed menarche or onset of puberty and dermatitis herpitiformis mouth. [1,11,12]

Screening for first degree relatives with CD or for other autoimmune conditions such as type-1 diabetes, autoimmune thyroiditis, autoimmune liver disease, selective IgA- deficiency and children with raised transaminases without known liver disease. Children with certain genetic conditions such as Down's, Williams and Turner syndromes are also at increased risk of developing CD. [1,11,12]

The diagnostic criteria for coeliac disease in children were first established by European Society of Paediatric Gastroenterology and Nutrition in 1969. It stated the 3-biopsy rule: i.e. to perform at least 3 small bowel biopsy (SBB), characteristic histological lesions in first SBB led to diagnosis of suspected Coeliac disease, but only after confirmation of histological relapse in third biopsy related to gluten challenge (GC), a definitive diagnosis of CD could be confirmed. These rules were followed for 20 years.[11]

Eventually development of anti endomysial antibodies (EMA) in 1980, with tissue transglutaminase antibodies (tTG) being recognized as the auto- antigen to CD led to identification of autoimmune nature of coeliac disease in 1990 which represented a true revolution in the field of coeliac disease with modification of the diagnostic criteria. The gluten challenge (GC) was now restricted to infants younger than 2 years at the first biopsy to exclude other causes of enteropathy or whenever the initial diagnosis was uncertain. These antibodies (EMA and tTG) have been observed to show a sensitivity and specificity of > 95%.

Additionally in the last few years, a strong association of CD with the genetic markers Human Leukocyte Antigen(HLA)-DQ2 and/or DQ8, which when combined reach a sensitivity of > 96% in most populations has been established. [2]

Arguably, the most important advance in classifying lesions in coeliac disease was forwarded by Marsh, [13] who proposed a series of interrelated lesions that integrates the pathophysiology of coeliac disease with its histopathological correlates. The Marsh grading system outlines four categories of lesions associated with coeliac disease: pre-infiltrative (type 0), infiltrative (type 1), infiltrative-hyperplastic (type 2) and flat-destructive (type 3); the atrophic-hypoplastic (type 4) lesion appears in later publications.[14] This system of grading assesses the presence of an immune response in the epithelium and describes the degree of architectural changes in the mucosa. This classification was revised to facilitate diagnostic applications, as the Marsh–Oberhuber grading system, which subcategorised type 3 lesions based on villous

height as type 3a mild atrophy, type 3b marked atrophy and type 3c total villous atrophy. [15]

Lately, critical voices have been claiming that in view of their higher diagnostic accuracy, specific antibody testing may replace the SBB in diagnostic procedure for Coeliac Disease. This histological lesions that are seen could be patchy sometimes and may occur in duodenal bulb only, and the interpretation depends on the preparation of tissue and is prone to a high interobserver variability. [4,16]

With improved accuracy of serological investigation and greater understanding of the spectrum of disease, the primacy of histopathology in confirming coeliac disease (CD) has been questioned.

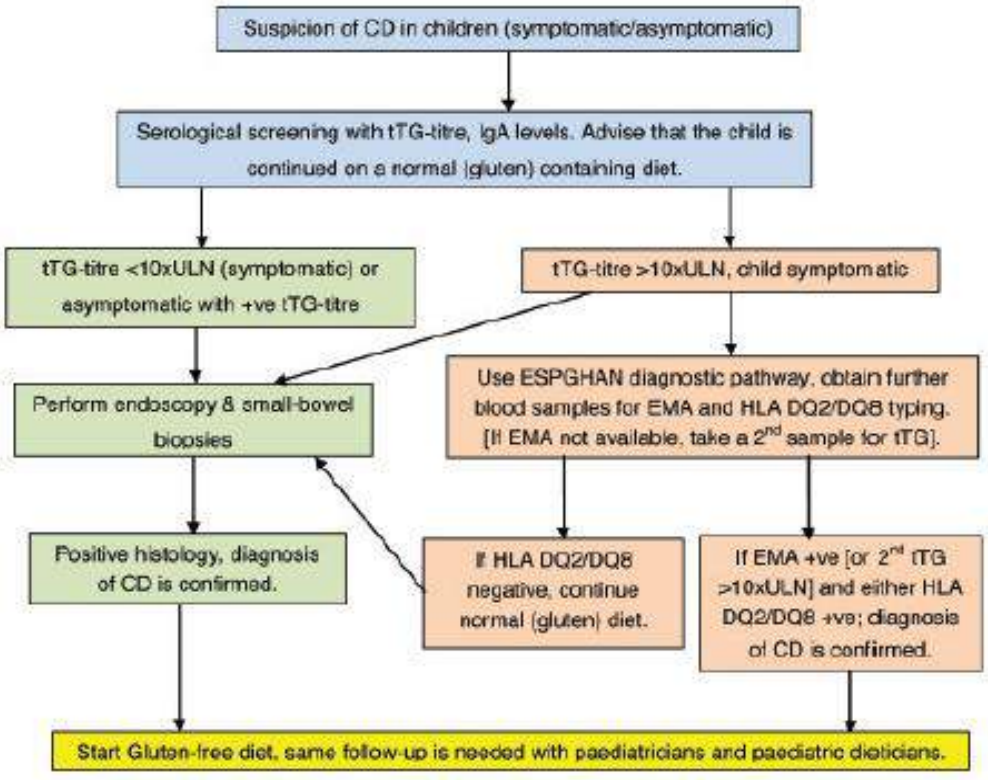
The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) has revised the approach for diagnosis of CD, in 2012[1]. Approach is towards a new definition of coeliac disease: it is a chronic disease, has multi-organ involvement, immune-mediated systemic disorder, gluten dependent clinical manifestations, transglutaminase-related i.e. anti-tissue transglutaminase antibodies (Anti-tTG), with small intestinal inflammation. [2,8]

Based on a number of paediatric studies including the confidential Avon Longitudinal Study of Parents and Children (ALSPAC) [17] prevalence of CD is currently considered to be around 1%. It is no longer considered to be a disease of the developed world and its widespread prevalence has been well documented in studies from developing countries. [18,19] Greater awareness and easier availability of serological testing has improved identification of CD, however, population studies show that up to 90% cases can remain undiagnosed. [20]

According to revised guidelines, the diagnosis of coeliac disease cannot rely on one single parameter, but on combination of clinical symptoms, CD-specific autoantibodies, histology, and genetics. A scoring system has been proposed but has to be formally evaluated in prospective clinical studies before it can be recommended in regular clinical use. [1]

ESPGHAN has modified the guidelines in 2012 and recommend that in symptomatic children, CD can be diagnosed without a biopsy when the IgA based anti-tissue transglutaminase (tTG) titre is > 10 x upper limit of normal (10 x ULN) and has HLA DQ2/8 positive serotype. [1] Figure 1 highlights an easy to follow algorithm.

A change in clinical practice (i.e. serologically diagnosing CD) even in context of developing countries should be evidence-based. CD is a diagnosis which needs commitment and adherence to lifelong Gluten-Free Diet (GFD); this is neither economical nor easily available in developing countries. It is, therefore, important to make the initial diagnosis of CD with reasonable certainty and the modified ESPGHAN guidelines (Figure 1) may be used in selective symptomatic patients with tTG-titres > 10 x ULN. [1]


Suspicion of CD in children (symptomatic/asymptomatic)
Serological screening with tTG-titre, IgA levels. Advise that the child is continued on a normal (gluten) containing diet.
tTG-titre <10xULN (symptomatic) or asymptomatic with +ve tTG-titre
tTG-titre >10xULN, child symptomatic
Perform endoscopy & small-bowel biopsies
Use ESPGHAN diagnostic pathway, obtain further blood samples for EMA and HLA DQ2/DQ8 typing. [If EMA not available, take a 2nd sample for tTG].
Positive histology, diagnosis of CD is confirmed.
If HLA DQ2/DQ8 negative, continue normal (gluten) diet.
If EMA +ve [or 2nd tTG >10xULN] and either HLA DQ2/DQ8 +ve; diagnosis of CD is confirmed.
Start Gluten-free diet, same follow-up is needed with paediatricians and paediatric dieticians.

Approach to symptomatic child

The implications of change of criteria will present a better outlook since there is omission of biopsy in selected cases as per these ESPGHAN guidelines.

It is important to understand that the modified ESPGHAN guidelines are currently not applicable to asymptomatic children (irrespective of tTG-titres) or other symptomatic children with tTG - titre < 10 x ULN. [1,12] These children will need endoscopy and small-bowel biopsies for a diagnosis of CD. [1] An isolated low-grade rise in tTG - titre can be found in conditions un-related to CD, such as viral infections (Coxsackie virus, Epstein- Barr virus), giardiasis, cow's-milk protein allergy, autoimmune diseases, antiphospholipid syndrome, tumors, liver disorders, inflammatory bowel diseases, myocardial damage, and psoriasis. [21]

The guideline recognizes the need to ‘‘perform prospective research studies’’ to support the reliability of recommendations before adoption of the guidelines into clinical practice. There are some retrospective studies done but there is paucity of application of these latest guidelines in clinical scenarios in India. In our study we want to assess the application of these latest ESPGHAN guidelines in children of our region for bringing an ease to the diagnosis of coeliac disease in the coming time.

AIMS AND OBJECTIVES

1. To evaluate triple test as a diagnostic criterion for coeliac disease.

REVIEW OF LITERATURE

Coeliac Disease (CD) is an immune mediated systemic disorder elicited by ingestion of gluten and related prolamines in genetically susceptible individuals and characterized by the presence of a variable combination of gluten dependent clinical manifestations and enteropathy. [11]

Over the last two decades, understanding of CD has changed from an uncommon enteropathy (incidence 1: 2500 - 3000) to a multi-organ disease with a strong genetic predisposition associated with HLADQ2/ DQ8. [1,12] Based on a number of paediatric studies including the confidential Avon Longitudinal Study of Parents and Children (ALSPAC). [17] prevalence of CD is currently considered to be around 1%. It is no longer considered to be a disease of the developed world and its widespread prevalence has been well documented in studies from developing countries. [18,19]

Upper endoscopy is a common procedure performed by gastroenterologists to investigate dyspepsia, dysphagia and other upper gastrointestinal symptoms. This offers an opportunity to obtain duodenal biopsies to establish or exclude the diagnosis of coeliac disease. Coeliac disease is increasingly detected by family physicians or gastroenterologists using immunoglobulin A anti-tissue transglutaminase antibody serology, which has operating characteristics perfectly suited for a screening test.

Greater awareness and easier availability of serological testing has improved identification of CD, however, population studies show that up to 90% cases can remain undiagnosed. [20]

CD can present with wide range of symptoms and can largely be divided into intestinal and extra-intestinal features. Intestinal features include diarrhoea, abdominal pain, bloating, weight loss and constipation. [1,11,12] Extra intestinal features include unexplained iron deficiency anaemia, short stature, faltering growth, constipation, liver disease, arthropathy, mouth ulcers, muscle weakness, delayed menarche or onset of puberty and dermatitis herpitiformis. [11,12]

Until recently, the diagnosis of CD in children has been based on small-bowel biopsies and histology (Marsh histological grading). [1,11]

Whether a biopsy is still required to confirm the diagnosis is debated, but in clinical practice, an endoscopy and biopsy is often performed to confirm the diagnosis. The serological titres are then often followed-up to assess adherence to gluten-free diet and adequate resolution of coeliac disease by diet. [22]

The diagnosis of coeliac disease requires a specific histopathological assessment. The mucosal architecture is the cornerstone of the histological classifications. Different confounding disorders should be considered in the differential diagnosis with coeliac disease. Dysbiosis could play a role in the activation of the immune system leading to the development of coeliac disease. [23]

Despite the knowledge of clinical, serological and histological typical lesions, there are some conditions to consider for differential diagnosis. From the first description of histology of CD, several studies were conducted to define similar findings suggestive for microscopic enteritis. Considering the establishment of early precursor lesions, the imbalance of gut microbiota is another point still requiring a detailed definition.

Freeman [24] reported a long experience of diagnosing coeliac disease using duodenal biopsies during upper endoscopy and the resultant increased diagnosis of coeliac disease in the population. Duodenal bulb biopsies may increase diagnostic yield because villous atrophy may be patchy. [25]

A recent study has shown that modern high-definition endoscopic techniques with image enhancement may be very accurate in diagnosing villous atrophy. [26] It may, therefore, be possible to only perform confirmatory duodenal biopsies, two from the duodenal bulb and four to six from the distal duodenum, where villous atrophy is suspected at high-definition endoscopy, with image enhancement techniques built into modern endoscopes.

Marsh modified type 1 histology grade may be missed by endoscopic techniques. Endoscopic and histological demonstration of villous

atrophy alone needs to be distinguished from other causes of villous atrophy. So, the duodenal biopsy is the gold standard for the diagnosis of coeliac disease. However, this approach requires considerable investment of time and resources by pathologists.

However, given improvements in the performance of serological testing, the possibility of accurately diagnosing CD without the need of a biopsy has attracted interest.

The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) published a guideline in January 2012 on diagnosis of coeliac disease (CD) in children. This guideline challenges the long-held paradigm that diagnosis of CD relies on the demonstration of typical histological findings on small intestinal biopsy. Within ESPGHAN, a working group was established to formulate new guidelines for the diagnosis of CD based on scientific and technical developments using an evidence-based approach.

The working group additionally developed a new definition of CD. CD is an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals and characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies HLA-DQ2 or HLA-DQ8 haplotypes, and enteropathy. CD-specific antibodies comprise autoantibodies against TG2, including endomysial antibodies (EMA), and antibodies against deamidated forms of gliadin peptides (DGP).

The guideline recommends that, for symptomatic patients with strongly positive coeliac serology (anti-TG2 >10 times the upper limit of normal [ULN] and positive EMA on separate blood test) and consistent HLA typing (HLADQ2 and/or -DQ8), the diagnosis of CD may be made without the need for small intestinal biopsy.[1]

CD may present with a large variety of nonspecific signs and symptoms. It is important to diagnose CD not only in children with obvious gastrointestinal symptoms but also in children with a less clear clinical picture because the disease may have negative health consequences. It has been estimated that only 1 in 3 to 1 in 7 adult patients with CD are symptomatic. [27] CD develops only after the

introduction of gluten-containing foods into a child's diet. The clinical symptoms of CD may appear in infancy, childhood, adolescence, or adulthood. A GFD in patients with CD improve or eliminates symptoms and normalizes the specific CD antibodies and histological findings. Therefore, a normal gluten-containing diet with normal quantities of bread, pasta, and other gluten-containing foods should be consumed until the end of the diagnostic process. This should be particularly emphasized to families that consume a low gluten-containing diet because of family members diagnosed as having CD. When the diagnosis of CD is suspected in patients who are already receiving a GFD, it is essential that they be placed on a gluten-containing diet before initiating the diagnostic process. The length of time of gluten exposure depends on the duration of the GFD. There is no evidence in the scientific literature to suggest the precise amount of gluten that needs to be ingested to elicit a measurable serological and/or intestinal mucosal response. [28] Patients without a conclusive diagnosis of CD, who are already receiving a GFD and do not want to reintroduce gluten into their diet, must be informed of the consequences of their decision.

The availability of serological tests with high accuracy and other diagnostic tests allows a firm diagnosis to be made. The interpretation and consequences of the test results differ between symptomatic and asymptomatic patients in at risk groups.

CD-specific antibody tests measure anti-TG2, EMA and anti-DGP. For the interpretation of antibody results, total IgA levels in serum, age of the patient, pattern of gluten consumption, and intake of immunosuppressive drugs should be considered. If gluten exposure was short or gluten had been withdrawn for a longer period (several weeks to years) the negative result is not reliable. For IgA-competent subjects, the conclusions should be drawn primarily from the results of IgA class antibody tests. For subjects with low serum IgA levels (total serum IgA<0.2 g/L), the conclusions should be drawn from the results of the IgG class CD-specific antibody tests.

Typing for HLA-DQ2 and HLA-DQ8 is a useful tool to exclude CD or to make the diagnosis unlikely in the case of a negative test result for

both markers. HLA testing should be performed in patients with an uncertain diagnosis of CD.

The histological features of the small intestinal enteropathy in CD have a variable severity, may be patchy, and in a small proportion of patients with CD appear only in the duodenal bulb. The alterations are not specific for CD and may be found in enteropathies other than CD. Biopsies should be taken preferably during upper endoscopy from the bulb (at least 1 biopsy) and from the second or third portion of duodenum (at least 4 biopsies). The pathology report should include a description of the orientation, the presence or not of normal villi or degree of atrophy and crypt elongation, the villus-crypt ratio, the number of intraepithelial lymphocytes (IELs), and grading according to the Marsh- Oberhuber classification.

A recent study from Pakistan highlighted an extremely important aspect of clinical practice - use of serological testing for diagnosing CD in children without a biopsy. [12] This is commendable considering the limited availability of resources in developing countries (e.g. unavailability of endoscopic facilities for children).[3] However, the study lacks a clear evidence-base as a single tTG-titre of > 3 x ULN was used for diagnosis of CD without HLA-DQ2/8 confirmation; it is unlikely to have wider applicability in similar set-ups. A tTG-titre of > 3 x ULN has not been found to be high enough to serologically diagnose CD in other published studies. [29,30,31,32]

The ESPGHAN has revised its recommendations to include a diagnostic algorithm that includes sequential serological testing and human leukocyte antigen genotyping for symptomatic children which would enable a diagnosis of coeliac disease to be made in the absence of a confirmatory intestinal biopsy.

Recent studies have evaluated the ESPGHAN guidelines and have mostly corroborated that coeliac disease can be accurately diagnosed in specific paediatric patient populations without the need of a biopsy. However, two cautionary points have been raised that warrant further consideration – the success of this approach is highly dependent targeting a population with a high pre-test probability of coeliac

disease, as well, the performance of serology assays must be established, and the appropriate use of cut-offs is essential.

A change in clinical practice (i.e. serologically diagnosing CD) even in context of developing countries should be evidence-based. CD is a diagnosis which needs commitment and adherence to lifelong GFD; this is neither economical nor easily available in developing countries. It is, therefore, important to make the initial diagnosis of CD with reasonable certainty and the modified ESPGHAN guidelines may be used in selective symptomatic patients with tTG-titres > 10 x ULN. [1] It is important to note that different laboratories have different normal ranges for tTG-titres and this should be taken into account while deciding the value corresponding to > 10 x ULN.

It is important to understand that the modified ESPGHAN guidelines are currently not applicable to asymptomatic children (irrespective of tTG-titres) or other symptomatic children with tTG-titre < 10 x ULN. [1,12] These children will need endoscopy and small-bowel biopsies for a diagnosis of CD.

A French study reported that the association between positive HLA-DQ2/DQ8 and serologic testing for CD has a high predictive value. Less than 1% of CD patients have negative HLA DQ2/DQ8 serotype and these children will need small-bowel biopsies for a diagnosis of CD.[33]

Similar genetic predisposition of HLA-serotype to CD was reported in another study from Pakistan with 49 children. [34] It is important to understand that a significant proportion of normal population has positive HLADQ2/DQ8 serotype and if they do not have symptoms of CD along with a normal tTG-titre, they do not have CD.[12]

The new ESPGHAN guidelines have been found to be applicable in low-resource settings when compared with very high tTG-titres and histological grading of biopsies were made in studies from Iran (pre-publication of ESPGHAN guidelines) and from India (post-publication of ESPGHAN guidelines). [21,35]

Paul et al.[36], therefore, suggested that in low-resource countries, symptomatic children with tTG-titres > 10 x ULN and positive Anti-

Endomysial Antibodies (EMA) can be diagnosed and managed as a case of CD. The joint BSPGHAN and Coeliac UK guidelines adapted from the 2012 ESPGHAN guidelines suggested that in centres where EMA is not available, a second tTG-titre may be used as an alternative while the child still remains on a gluten-containing diet; the repeat tTG-titre also needs to be > 10 x ULN. [11]

This is also supported by a study from India with 333 children where tTG-titre was found to be a highly sensitive and specific serologic marker. The authors also suggested that as tTG-titre analysis is technically simpler and has high concordance with EMA, it can be used as an alternative to EMA in developing countries. [37]

Attempt should be made to send a HLA DQ2/DQ8 sample, applicability and usefulness of which has previously been established in a study from Pakistan. [34]

Bishop et al. [38] concluded in a prospective study that the ESPGHAN guideline performs well in New Zealand Children population that the adoption of the guideline would reduce the number of patients requiring endoscopy without compromise in diagnostic accuracy. In this study histological findings according to Marsh criteria were correlated with blood results and the accuracy of the guideline was analysed. The study also examined the role of deamidated gliadin peptide (DGP) in the diagnosis of CD. For symptomatic patients with consistent HLA subtypes, strongly positive serology (as described in the ESPGHAN guidelines) accurately predicted biopsy-proven CD in >95% of cases. DGP was positive in fewer patients than anti-TG2 or EMA. Incorporation of DGP as a second confirmatory serological test in place of EMA was associated with maintained predictive value of guideline, but fewer patients fulfilling criteria for biopsy-free diagnosis. The involvement of paediatric gastroenterological expertise, however, remains key to diagnosis of CD.

The main conclusions of these guidelines are that the diagnosis of CD depends on gluten-dependent symptoms, CD-specific antibody levels, the presence of HLA-DQ2and/or HLA-DQ8, and characteristic histological changes (villous atrophy and crypt hyperplasia) in the

duodenal biopsy. High TG2-antibody levels 10 times ULN for a standard curve-based calculation) as measured by a qualified laboratory show high diagnostic accuracies. In the presence of high antibody levels the diagnosis of CD may be based on a combination of symptoms, antibodies, and HLA, thus omitting the duodenal biopsy. The diagnosis is confirmed by an antibody decline and preferably a clinical response to a GFD. Gluten challenge and repetitive biopsies will be necessary only in selected patients in whom diagnostic uncertainty remains.

The present guidelines replace the existing ESPGHAN guidelines but require a period of implementation and testing. [(36)] It will be important to be precise in the clinical evaluation of patients and to perform prospective research studies. Likewise, it will be important for laboratories performing analyses of CD antibodies and HLA determinations to develop methodologies and continuously participate in quality control programmes. In the future, new diagnostic tools, for example a new serological test, may be evaluated in symptomatic patients with CD and controls that are defined and classified by all 4 diagnostic criteria (symptoms/signs, antibodies, HLA, and histology. Based on the current evidence symptoms, CD-specific antibodies, HLA, and biopsy findings contribute to the CD diagnosis. A wide spectrum of findings is present within each item, from suggestive to contradictory. For example, a malabsorption syndrome is more convincing than alopecia or being a person belonging to a risk group. Likewise, histological lesions with severe villous atrophy (Marsh 3b and 3c) are more convincing than Marsh 1 lesions. In the hierarchy of antibodies, EMA has the highest impact, whereas negativity for all antibodies on an unrestricted diet or absence of both HLA-DQ2 and HLA-DQ8 strongly contradict the presence of CD.

Nonetheless, an unconventional HLA-DQ type cannot totally exclude CD, and typical gluten-responsive lesions can be present even in the absence of CD antibodies in serum. A scoring system may be applied so that a stronger finding in 1 item may compensate for a missing abnormality in another and the sum could be taken into account. The

main functions of a scoring approach are to assist in the interpretation of the spectrum of diagnostic findings and to protect against over diagnosis in insufficiently documented or borderline cases. In addition, the scoring system may provide further. In addition, the scoring system may provide further diagnostic reassurance in typical cases in which genetic testing or immunohistochemistry are not available. Such scoring systems must be evaluated formally in prospective study.

S. Hubsy et al. [1] for the ESPGHAN working group on coeliac disease diagnosis on behalf of the ESPGHAN Gastroenterology committee made a panel of 17 experts & defined Coeliac disease and developed new diagnostic criteria based on the Delphi process. Two groups of patients were defined as children with symptoms suggestive of CD in group 1 and asymptomatic children at increased risk for CD in group 2. In group 1, the diagnosis of CD is based on symptoms, positive serology, and histology that is consistent with CD. If IgA anti-tissue transglutaminase type 2 antibody titres are high >10 times the upper limit of normal, then the option is to diagnose CD without duodenal biopsies by applying a strict protocol with further lab tests. In group 2, the diagnosis of CD is based on positive serology, and histology. HLA DQ2 & DQ8 testing is valuable because CD is unlikely if both halotypes are negative.

Now the gluten challenge and biopsies will be necessary only in selected patients in whom diagnostic uncertainty remains.

Gabriela Klapp et al. [(39)] wrote an abstract on application of ESPGHAN guidelines where they did a retrospective review of all patients suspected of having CD who had undergone a small bowel biopsy. All symptomatic children with serological markers positive were included in the study. Out of them, 116 were positive for the triple test serological markers positive, 113 of 116 had a Marsh 2/3 histological lesion and had been considered to have CD. Thus, positive predictive value of triple test was 97.4%. The other 3 cases (2.6 %) had Marsh 0/1 lesion, and were considered false positive, however on follow up, all 3 children developed histological damage after a gluten challenge test. Finally, the positive predictive test for triple test was 100%. The authors

commented that in low resource countries, these guidelines were applicable in symptomatic children with TT positivity and a diagnosis of coeliac can be easily established in them.

P.G. Hill et al. [40] did a study where he said that in view of high diagnostic accuracy of Immunoglobulin, anti-tTG for detecting coeliac disease, a small biopsy is not always needed. The anti –tTG antibody gives a positive predictive value of 100%. They also commented that biopsies showing mild histopathological lesions are difficult to interpret. They had used the cut off >10times the upper limit of anti-tTg. As per them 58% of 112 new diagnoses had levels above this cut off and biopsy was not needed in them.

Jonathan Bishop et al.[38] concluded in a prospective study that the ESPGHAN guideline performs well in New Zealand Children population. Adoption of the guideline would reduce the number of patients requiring endoscopy without compromise in diagnostic accuracy. In this study histological finding according to Marsh criteria were correlated with blood results and the accuracy of the guideline was analyzed. The study also examined the role of deamidated gliadin peptide (DGP) in the diagnosis of CD. For symptomatic patients with consistent HLA subtypes, strongly positive serology (as described in the ESPGHAN guidelines) accurately predicted biopsy-proven CD in >95% of cases. DGP was positive in fewer patients than anti-TG2 or EMA. Incorporation of DGP as a second confirmatory serological test in place of EMA was associated with maintained predictive value of guideline, but fewer patients fulfilling criteria for biopsy-free diagnosis. The involvement of paediatric gastroenterological expertise, however, remains the key to the diagnosis of CD.

ESPGHAN guidelines for diagnosing Coeliac Disease 2020 [41] recommend considering testing for CD in children and adolescents with symptoms like constipation, abdominal pain, signs of irritable bowel syndrome (IBS), dyspepsia more as compared with the general population. Extraintestinal symptoms like weight loss, failure-to-thrive stunted growth/ short stature, delayed puberty, amenorrhea, irritability, chronic fatigue, neuropathy, arthritis/arthralgia chronic iron-deficiency

anaemia, decreased bone mineralization (osteopenia/osteoporosis), repetitive fractures, recurrent aphthous stomatitis, dermatitis herpetiformis–type rash, dental enamel defects, abnormal liver biochemistry and specific conditions like first-degree relatives with CD, autoimmune conditions: T1DM, thyroid disease, liver disease, Down syndrome, Turner syndrome William's-Beuren syndrome

IgA deficiency should also be considered for testing of CD. HLA-DQ2 and DQ-8 typing is not required in patients with positive TGA-IgA, if they qualify for CD diagnosis with biopsies or have high-serum TGA-IgA ≥ 10 x ULN and EMA-IgA positivity. If a patient tests negative for HLA DQ2 and DQ8, the risk of CD is very low, whereas a positive result does not confirm the diagnosis. These guidelines recommend testing for total IgA and TGA-IgA as initial screening in children with suspected CD. In patients with low total IgA concentrations, an IgG-based test (DGP, EMA or TGA) should be performed as a second step. Testing for EMA, DGP or AGA antibodies (IgG and IgA) as initial screening in clinical practice is not recommended. It was recommend that for CD diagnosis without biopsies, TGA- IgA

serum concentration of at least 10 x ULN should be obligatory. The guidelines recommend that in children with TGA ≥ 10 x ULN, and parents/patient agreement to the no-biopsy approach, the CD diagnosis should be confirmed by a positive EMA-IgA test in a second blood sample. These guidelines also recommend that the decision to omit upper endoscopy with biopsies can be taken without the consideration of missing other pathologies or diagnoses

Summary

The duodenal biopsy will remain the gold standard for diagnosing coeliac disease in most patients. However, as serology assays evolve and as a greater understanding of the genetic risk factors of coeliac disease is achieved, more patients may be accurately diagnosed without the need for a biopsy. [28]

Materials and Methods

It was a prospective observational study of one year and six months i.e. from 1st November 2018 to 30th April 2020. Children of age group 1 year to 18 years coming to the Paediatric G.I. clinic OPD & IPD of Department of Paediatrics at DMC&H, Ludhiana.

STUDY DESIGN

It was a prospective observational study over a period of eighteen months from 1st November 2018 to 30th April 2020

SOURCE OF DATA

This study was conducted in the department of Paediatrics in Dayanand Medical College and Hospital, Ludhiana, Punjab. All cases presenting with intestinal and extra-intestinal symptoms suggestive of coeliac disease aged 1 to 18 years were assessed for diagnosis of coeliac disease and relevant data was collected on a pre-structured proforma after taking due consent from the patients legally authorized representative or guardian. Proforma contained information regarding the demographic and clinical parameters. Proforma also included a scoring system which aids the diagnosis of coeliac disease. (Appendix-1)

A total of 56 patients were included in the study out of which 38 were males and 18 were females. None of the children taken were on gluten free diet.

INCLUSION CRITERIA

Children from 1 year to 18 years of age.

All children coming in OPD & IPD will be included.

Children with symptoms suggestive of coeliac disease

Serological marker positivity of Anti-tTG, EMA, HLA DQ2/DQ8

EXCLUSION CRITERIA

Children below 1 year of age.

Serological Markers negative

Asymptomatic children diagnosed otherwise.

Patient or parents not giving consent for the study.

Methodology

Diagnosis of coeliac disease was based on revised ESPGHAN criteria.

ESPGHAN Criteria

According to ESPGHAN guideline, biopsy may be avoided in symptomatic patients with anti-TG2 >10 times ULN, positive EMA, and coeliac-susceptible HLA haplotype [(1)].

Clinical features:

CD can present with wide range of symptoms and can largely be divided into intestinal and extra-intestinal features.

Intestinal features include diarrhoea, abdominal pain, bloating, weight loss and constipation.[(1-3)]

Extra-intestinal features include unexplained iron deficiency anaemia, short stature, faltering growth, constipation, liver disease, arthropathy, mouth ulcers, muscle weakness, delayed menarche or onset of puberty and dermatitis herpitiformis.[(1-3)]

A number of asymptomatic children will be diagnosed with CD following screening for first degree relatives with CD or for other autoimmune conditions such as type-1 diabetes, autoimmune thyroiditis, autoimmune liver disease, selective IgA-deficiency, and children with raised transaminases without known liver disease.[(1-3)] Children with certain genetic conditions such as Down's, Williams and Turner syndromes are also at increased risk of developing CD.[(1,3)]. These asymptomatic children were not included in this study.

Serologic Testing

10 mL of blood was drawn and analyzed for total IgA, anti-TG2, EMA, HLA-DQ2/-DQ8

Anti-TG2. Serum anti- tissue transglutaminase levels were measured by EliA (Enzyme Linked Immuno Assay) Phadia 250 by Thermo Fischer scientific. A value of less than 7 U/ml was considered normal, 7 to 10U/ml was considered equivocal and a value of more than 10 U/ml was considered positive. The level above 100 U/mL were considered as >10 times the upper limit of normal ULN

EMA testing: It was performed using IgA endomysial antibody assay by indirect immunofluorescence, using Immco Diagnostic slides

(primate smooth muscle substrate, reference 2160) and an INOVA fluorescein-labeled IgA conjugate Anti-endomysium antibodies are diagnostically sensitive and specific for coeliac disease. Interpretation: +1 positivity denotes minimum immunofluorescence of no significance, +2 positivity denotes weak and clinically insignificant positivity, +3 denotes strong positivity but requires clinical correlation and + 4 denotes strong positivity highly suggestive of coeliac disease.

HLA Serotypes: HLA molecular typing was done using real time PCR method.

Duodenal Biopsies: At least 1 biopsy was taken from duodenal bulb (cap) and at least 4 biopsies from second or third part of the duodenum at endoscopy [(1)]. All biopsies were reported by a single histopathologist. Histology was considered diagnostic if crypt hypertrophy and/or villous atrophy were observed (modified Marsh criteria grade 2 and above) [(8)].

Modified Marsh Classification of histologic findings in coeliac disease (Oberhuber)

Marsh Type	IEL / 100 enterocytes – jejunum	IEL / 100 enterocytes – duodenum	Crypt hyperplasia	Villi
0	<40	<30	Normal	Normal
1	>40	>30	Normal	Normal
2	>40	>30	Increased	Normal
3a	>40	>30	Increased	Mild atrophy
3b	>40	>30	Increased	Marked atrophy
3c	>40	>30	Increased	Complete atrophy

IEL/100 enterocytes, intraepithelial lymphocytes per 100 enterocytes

Type 0: Normal; coeliac disease highly unlikely.

Type 1: Seen in patients on gluten free diet (suggesting minimal amounts of gluten or gliadin are being ingested); patients with

dermatitis herpetiformis; family members of coeliac disease patients, not specific, may be seen in infections.

Type 2: Very rare, seen occasionally in dermatitis herpetiformis.

Type 3: Spectrum of changes seen in symptomatic coeliac disease.

Triple test and biopsy were done to diagnose the coeliac disease. Triple test positivity was defined to be anti-tTG >10 times ULN, EMA positivity of ≥ +2 and either or both HLA DQ2/8 positive serotype. Biopsy done were graded as per modified Marsh criteria. Grade 2 and above were considered diagnostic.

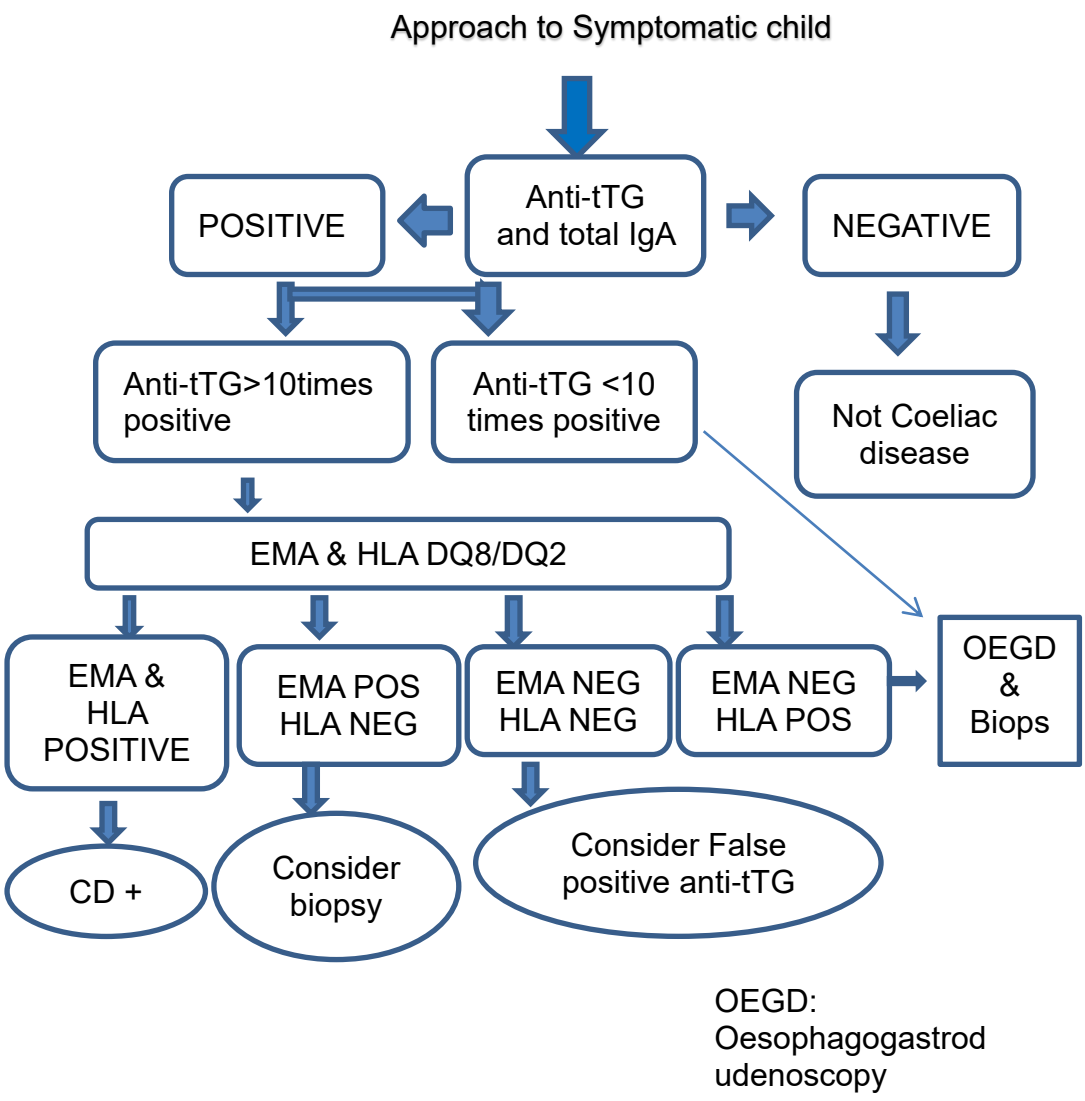
Scoring System as per the ESPGHAN

The scoring takes into account 4 items: symptoms, antibodies, HLA, and biopsy findings, each contributing once. To make the diagnosis, a sum of 4 points is required

Parameter	Description	Score
Symptoms	Malabsorption	2
	Associated Conditions	1
	Asymptomatic	0
Serum Antibodies	EMA positivity and/or Anti-TG2 >10 times	2
	Low Anti-TG2 or EMA	1
	Serology was not performed	0
	Serology performed but all_ coeliac-specific antibodies negative	-1
HLA	Full HLA-DQ2 or HLA-DQ8 heterodimers present	1
	No HLA performed or half DQ2 present	0
	HLA neither DQ2 nor DQ8	-1
Histology	Marsh 3b or 3c (subtotal villous atrophy, flat lesion)	2
	Marsh 2 or 3a (moderately decreased villus height/crypt depth ratio) or Marsh 0–1 plus intestinal TG2 antibodies	1
	Marsh 0-1 OR no biopsy performed	0

Serological tests were compared with histological findings to assess the diagnostic accuracy of the ESPGHAN guideline

OUTCOME: This study assessed the new ESPGHAN guidelines and their use in diagnosis of coeliac disease with less need of biopsy in serology positive patient.



OEGD: Oesophagogastrodudenoscopy

Apart from the information regarding diagnosis of coeliac disease, demographic parameters, clinical features and physical findings in children were noted. Age, sex, socio-economic status, weight, height, body mass index, general physical examination, positive systemic findings, age at the time of diagnosis were recorded.

Various investigations done at the time of diagnosis were also noted.

Socio-economic scale – Modified kuppuswamy scale – 2014 version (shown in annexure) was used to classify the families into different grades of socio – economic status.

Weight – weight in kilograms was plotted on WHO IAP growths charts (as shown in annexure) for males and females and was interpreted as – (For less than 5 years)

Less than 3rd percentile

3^{rd} to 50^{th} percentile

50^{th} to 97^{th} percentile

(For more than 5 years)

Less than 3rd percentile

3^{rd} to 10^{th} percentile

10^{th} to 25^{th} percentile

25^{th} to 50^{th} percentile

50th to 75^{th} percentile

75^{th} to 90^{th} percentile

More than 97^{th} centile

Height – height in centimeters was plotted on WHO IAP (as shown in annexure) growth charts for males and females and was interpreted as-

(For less than 5 years)

Less than 3rd percentile

3^{rd} to 50^{th} percentile

50^{th} to 97^{th} percentile

(For more than 5 years)

Less than 3rd percentile

3^{rd} to 10^{th} percentile

10^{th} to 25^{th} percentile

25^{th} to 50^{th} percentile

50th to 75^{th} percentile

75^{th} to 90^{th} percentile

More than 97^{th} centile

Height less than 3rd percentile for age – according to WHO IAP growth chart, was taken as short stature.

B.M.I. (Body mass index) – B.M.I. kilograms/square of height in meters was plotted on WHO growths charts (as shown in annexure) for males and females and was interpreted as –

Less than 3rd percentile

3^{rd} to 10^{th} percentile

10^{th} to 25^{th} percentile

25^{th} to 50^{th} percentile

STATISTICAL ANALYSIS:

Data was described in terms of range; mean ±standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. For comparing categorical data, Chi square ($\chi 2$) test was performed and exact test was used when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant.

All statistical calculations was done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Window.

OBSERVATION AND RESULTS

This prospective observational study was conducted in the department of Paediatrics in Dayanand Medical College and Hospital, Ludhiana, Punjab over a period of one year and six months i.e. from 1st November 2018 to 30th April 2020. Children of age group 1 year to 18 years coming to the Paediatric G.I. clinic OPD & IPD were included in the study.

All cases of suspected coeliac disease aged 1 to 18 years were assessed for diagnosis of coeliac disease and relevant data was collected on a pre-structured proforma after taking due consent from the patients legally authorized representative or guardian.

Diagnosis of coeliac disease was based on revised ESPGHAN criteria. Triple test and biopsy were done to diagnose the coeliac disease.

Apart from the information regarding diagnosis of coeliac disease, demographic parameters, clinical features and physical findings in children were noted. Age, sex, socio-economic status, weight, height, body mass index, general physical examination, positive systemic findings, age at the time of diagnosis were recorded.

A total of 56 children presented to us with signs and symptoms pertaining to coeliac disease out of which 44 children met inclusion criteria for this study and the following observations were made.

Table 1: Age Distribution (n=44)

Age Group	Number of cases	Percentage
< 3	5	11.4
3-5	15	34.2
6-8	9	20.4
9-11	6	13.6
12-14	6	13.6
≥15	3	6.8
Total	44	100%
Mean ± SD	7.02 ± 4.07	

Table 1 shows the age wise distribution of the children in this study. The age range in this study was 1.5 to 15 years. Maximum number of children belonged to the age group 3-5 years (34.2%). Only 3 children with age of 15 years were included in this study. The mean age in this study was 7.02 with a standard deviation of 4.07 years.

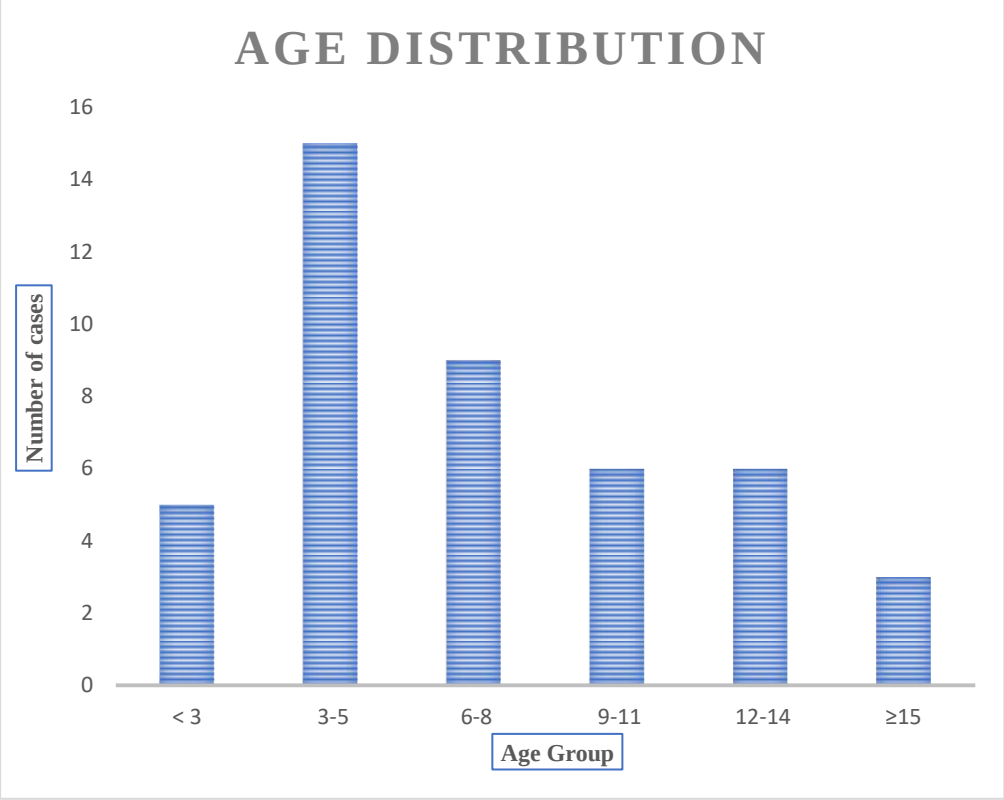


Figure 1: Age Distribution of cases

Table 2: Gender Distribution (n=44)

Gender	Number of cases	Percentage
Female	15	34
Male	29	66
Total	44	100%

In this study, most of the patients were males i.e. 29 (66%) and 15 (34%) were females as shown. Male to female ratio was 1.93:1.

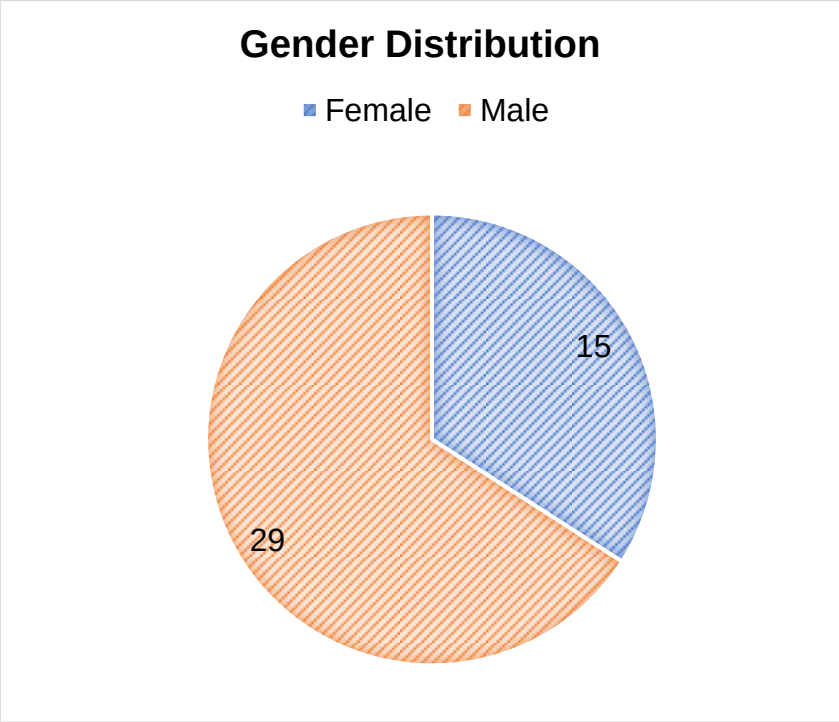


Figure 2: Gender Distribution of cases

Table 3: Gender distribution in different age groups (n=44)

Age Group	Males	Females
< 3	4	1
3-5	10	5
6-8	5	4
9-11	4	2
12-14	3	3
≥15	3	0
Total	29	15

Table 3 shows the age group wise male and female distribution. The age was not normally distributed in this study (Shapiro-Wilk Test: p = 0.003). The mean age was 7.02 (4.07). The median (IQR) age was 6.00.

Among females, maximum cases were in age group of 3 to 5 years i.e. 5/15 (33.3%), followed by 6 to 8 years group i.e. 4/15 (26.7%) and 3 patients in 12 to 14 years age group.

Among males, maximum cases were in the age group of 3 to 5 years i.e. 10/29 (34.5%), followed by 5 (17.2%) patients in 6 to 8 years group, 4 patients (13.8%) each in less than 3-year age group and 9 to 11 years group. There were 3 patients in 12-14-year age group and 3 patients were 15-year-old. There was no statistically significant difference in the gender distribution among various age groups.

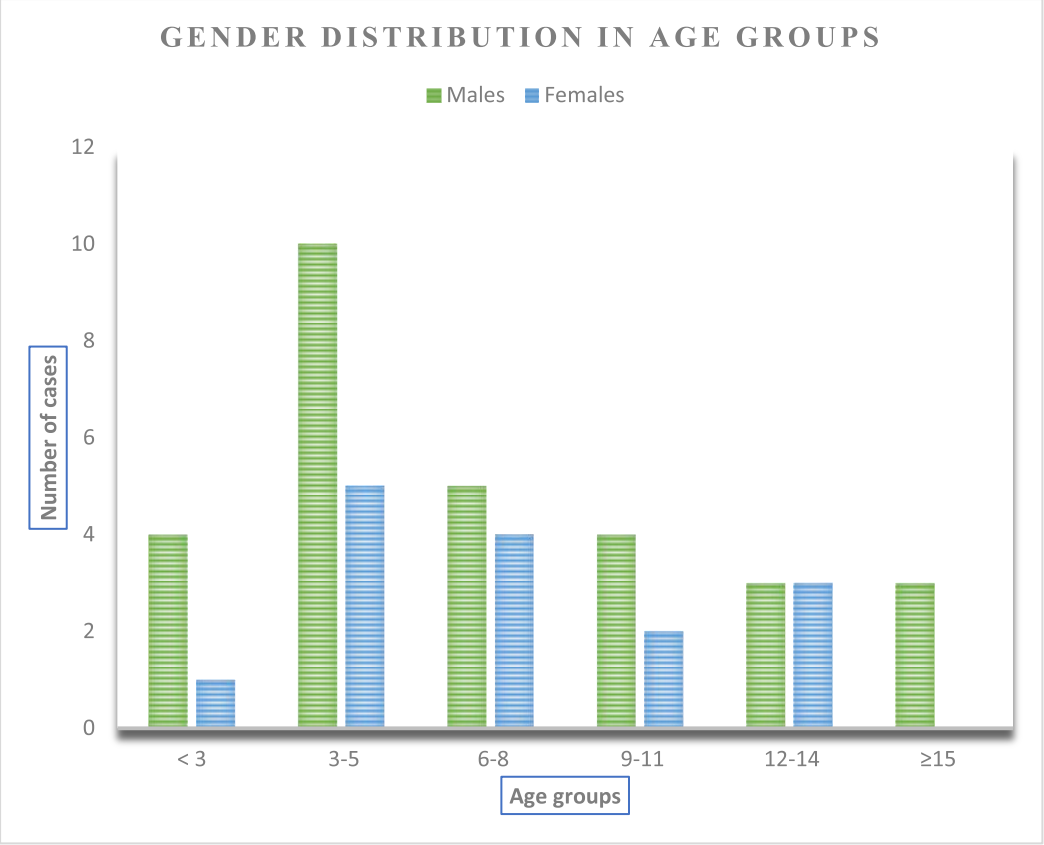


Figure 3: Gender Distribution in different age groups of cases

Table 4: Socio-Economic Distribution (n=44)

Socio-Economic Class	Total Number	Percentage %
Lower Class	1	2.3
Lower Middle Class	14	31.8
Upper Class	1	2.3
Upper Middle Class	28	63.6
Total	44	100

Modified Kuppuswamy scale (2014) was used to assess the socio-economic status of families of children with coeliac disease. Majority of patients belonged to middle class group, i.e 63.6% in upper middle-class group and 31.8% in lower middle-class group. Lower class and upper class had only 2.3% of children each.

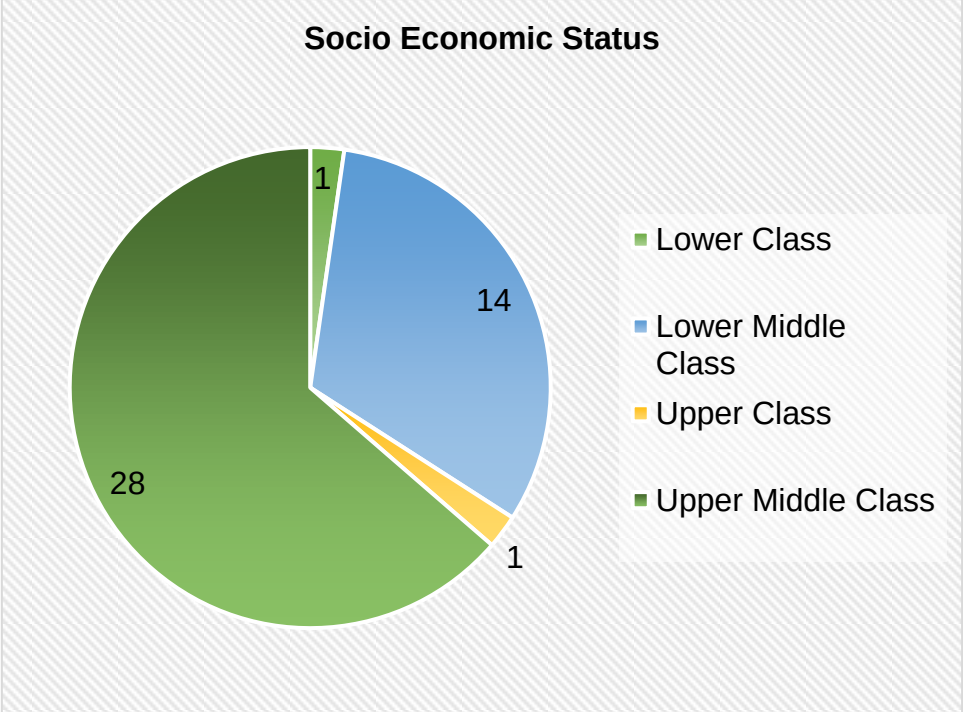


Figure 4: Distribution in terms of socio economic status of the families

Table-5: Presenting complaints at the time of diagnosis

Presenting Complaints	Number of patients (percent)
Pain Abdomen	40 (90.9%)
Loose Stools	11 (25.0%)
Constipation	25 (56.8%)
Loss Of Appetite	23 (52.3%)
Poor Weight Gain	25 (56.8%)
Vomiting	7 (15.9%)

Table 5 shows that the pain abdomen was the most common presenting complaint present in 90.9% of the patients followed by constipation and poor weight gain which was present in 56.8% of the patients. Loss of appetite was present in 52.3% of patients and loose stools were presenting complaint in 25% of the patients. Only 7% of the patients in this study presented with vomiting.

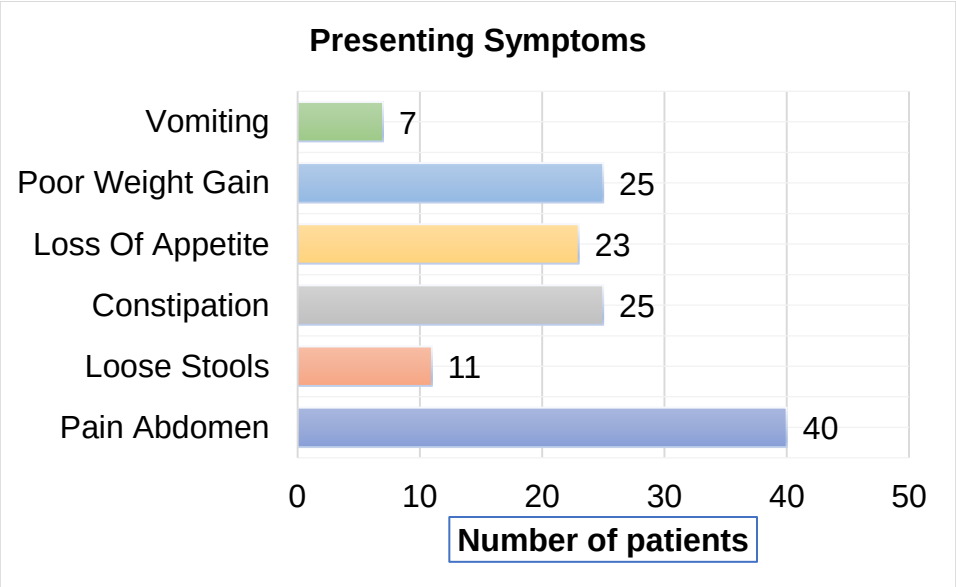


Figure 5: Symptoms of the patients at the time of diagnosis

Table 6: Associated conditions at the time of diagnosis

Associated Conditions	Number of patients (percent)
Anaemia	40 (90.9%)
Asthma	6 (13.6%)
Hypothyroidism	1 (2.3%)
Allergic Disorder	7 (15.9%)
Type 1 DM	1 (2.3%)
Ventricular Septal Defect	1 (2.3%)
Vitamin D Deficiency	32 (72.7%)

Children with coeliac disease were screened for other associated autoimmune and systemic conditions at the time of diagnosis. Above table shows that 90.9% children in the study were anaemic. Among 44 children 7 (15.9%) had some associated allergic disorder, 6 children (13.6%) had bronchial asthma, 32 children (72.7%) had associated Vitamin D deficiency. Type 1 DM was diagnosed in 1 child. Ventricular septal defect was also diagnosed in 1 child. Only 1 child in this study was hypothyroid.

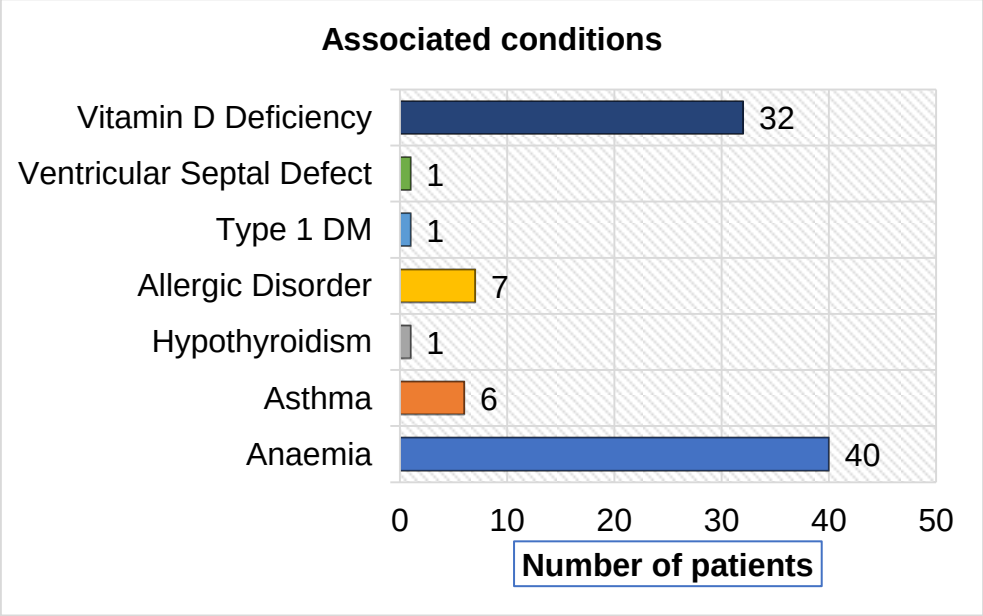


Figure 6: Associated conditions at the time of diagnosis.

Table 7: Distribution of patients in terms of family history (n=44)

Family History	Number of patients	Percentage
Present	4	9.1%
Absent	40	90.9%
Total	44	100.0%

Coeliac disease has a proven genetic predisposition. In this study, 4 patients (9.1%) with coeliac disease had positive family history of coeliac disease. Among then 3 were first degree relatives, 1 was second degree relative. But majority of the children, i.e. 90.9%, did not have history of coeliac disease in their families.

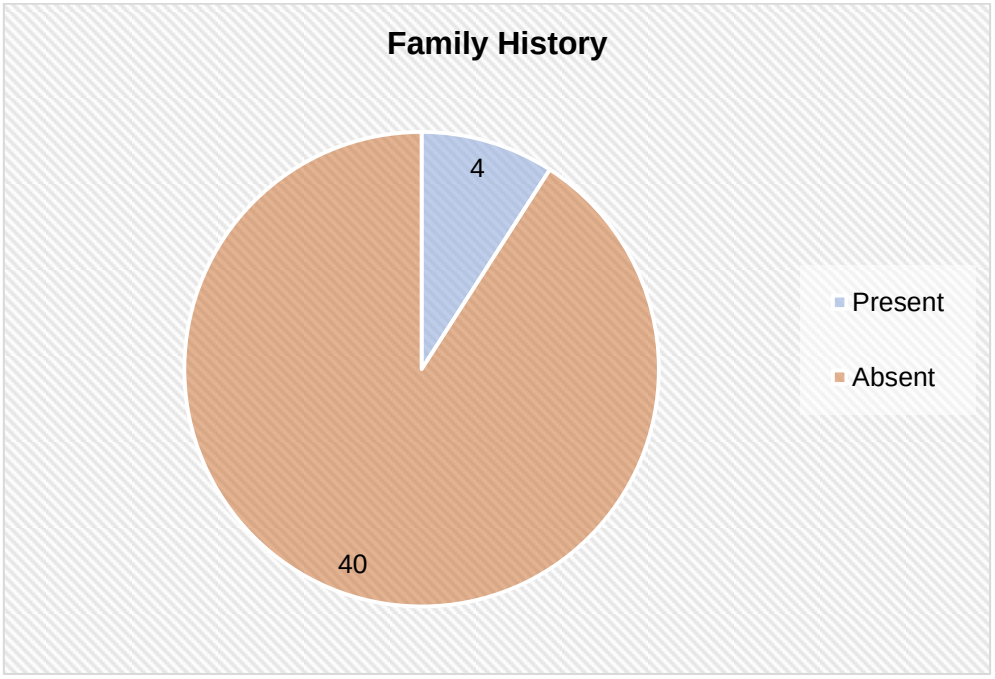


Figure 7: Distribution of patients in terms of family history

Table 8: General physical examination of children with coeliac disease

Examination	Number of cases
Pallor	44 (100.0%)
Rickets	1 (2.3%)
Skin Changes	3 (6.8%)
Nail Changes	18 (40.9%)

In this study, pallor was present in all the children. One child had rickets, 3 had skin changes and 18 children had associated nail changes.

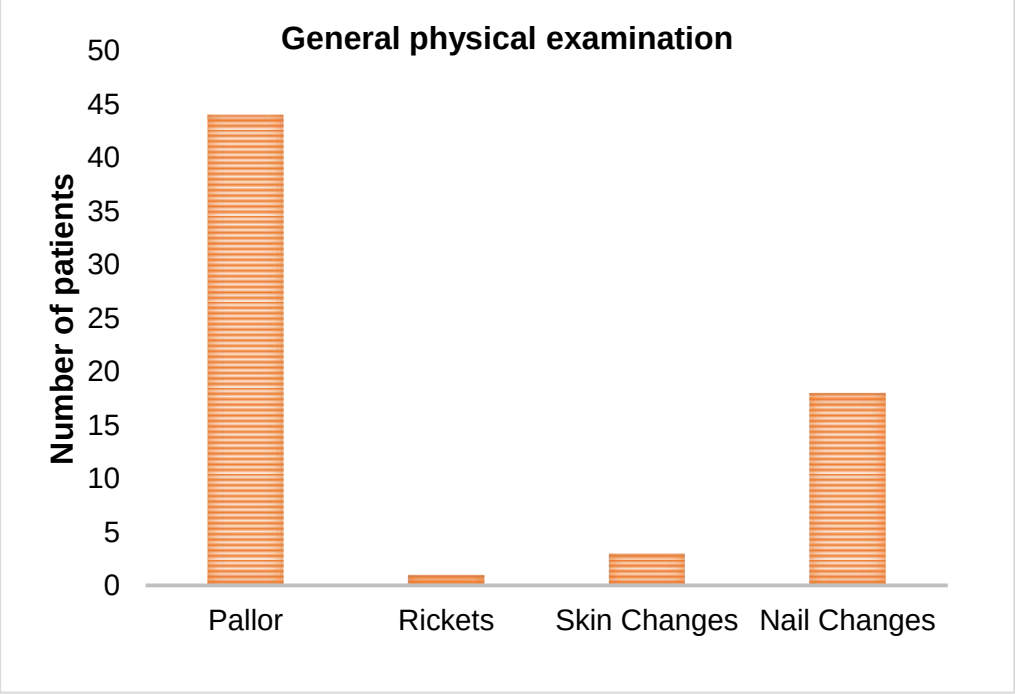


Figure 8: General physical examination of children with coeliac disease

Table 9: Weight inference of the children with coeliac disease

Weight Inference	Number of cases (percentage)
<5 Years: 17 (38.6%)	
<3rd Centile	3 (6.8%)
3rd-50th Centile	14 (31.8%)
>5 Years: 27 (61.4%)	
<3rd Centile	5 (11.4%)
3rd-10th Centile	14 (31.8%)
10th-25th Centile	8 (18.2%)

Detailed anthropometry was done in all the children and the parameters compared with standard WHO IAP charts. In children less than 5 years of age, 3/44 (6.8%) children had weight less than 3rd percentile and 14/44 (31.8%) children had weight between 3rd to 50th percentile.

In children more than 5 years of age, 5/44 (11.4%) children had weight less than 3rd percentile, 14/44 (31.8%) children had weight between 3rd to 10th percentile and 8/44 (18.2%) children had weight between 10th to 25th percentile. Majority of children had weight less than 50th percentile.

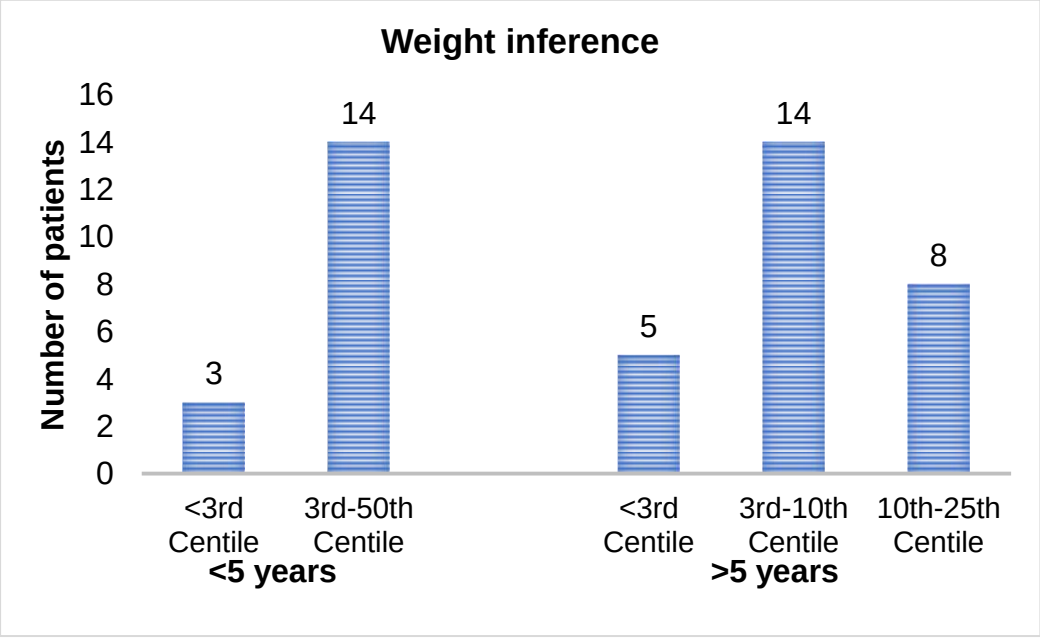


Figure 9: Weight inference of the children with coeliac disease

Table 10: Height inference of the children with coeliac disease

Height Inference	Number of cases (percentage)
<5 Years: 17 (38.6%)	
<3rd Centile	5 (11.3%)
3rd-50th Centile	12 (27.3%)
>5 Years: 27 (61.4%)	
<3rd Centile	3 (6.8%)
3rd-10th Centile	12 (27.3%)
10th-25th Centile	12 (27.3%)

Table 10 shows the inference of height of children with coeliac disease according to WHO IAP growth charts. In age group less than 5 year, 5/44 (11.4%) children had height less than 3rd percentile and 12/44 (27.3%) children had height between 3rd to 50th percentile.

In age group of children more than 5 years, 6.8% of the children had height less than 3rd centile, 27.3% of the children had height and 3re centile and 10^{th} centile and rest 27.3% of the children had height between 10^{th} and 25^{th} centile. All the children had height less than 50th percentile.

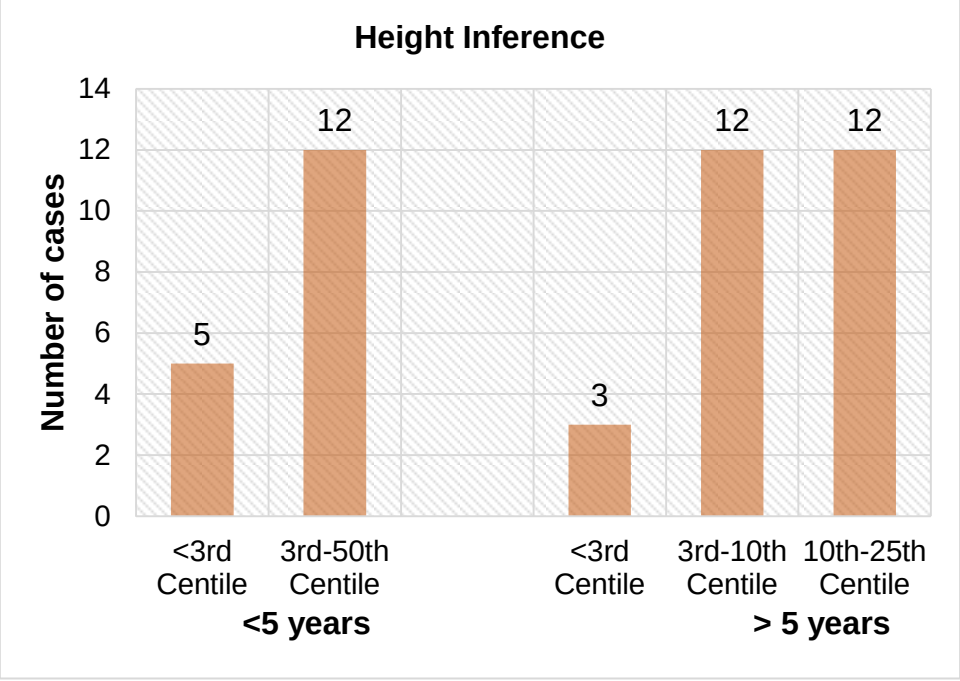


Figure 10: Height inference of the children with coeliac disease

Table 11: Distribution of the Patients in Terms of Haemoglobin (g/dL)

Haemoglobin (g/dL)	
Mean ±SD	10.64 ±1.71
Median (IQR)	10.75 (2.62)
Range	7.4 - 14.5

The variable haemoglobin (g/dL) was normally distributed (Shapiro-Wilk Test: p = 0.308).

The mean (SD) of haemoglobin (g/dL) was 10.64 (1.71). The median (IQR) of haemoglobin (g/dL) was 10.75 (2.62). The haemoglobin (g/dL) ranged from 7.4 - 14.5.

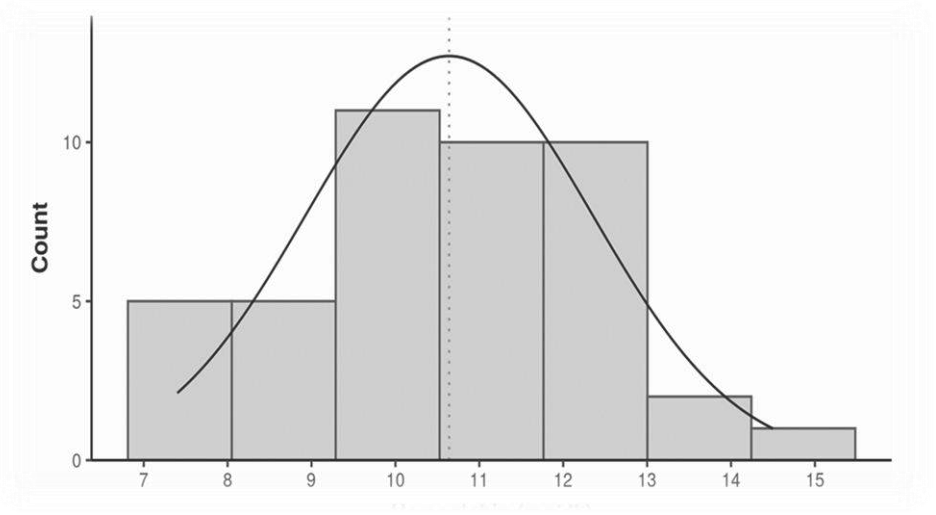


Figure 11: Distribution of the Patients in Terms of Haemoglobin

Table 12: Distribution of the Patients in Terms of TLC (10^3/cu.mm)

TLC (10^3/cu.mm)	
Mean (SD)	8.62 (2.48)
Median (IQR)	8 (3.75)
Range	4.7 – 16

The variable TLC (10^3/cu.mm) was not normally distributed (Shapiro-Wilk Test: p = 0.049). The mean (SD) of TLC (10^3/cu.mm) was 8.62 (2.48). The median (IQR) of TLC (10^3/cu.mm) was 8.00 (3.75). The TLC (10^3/cu.mm) ranged from 4.7 - 16.

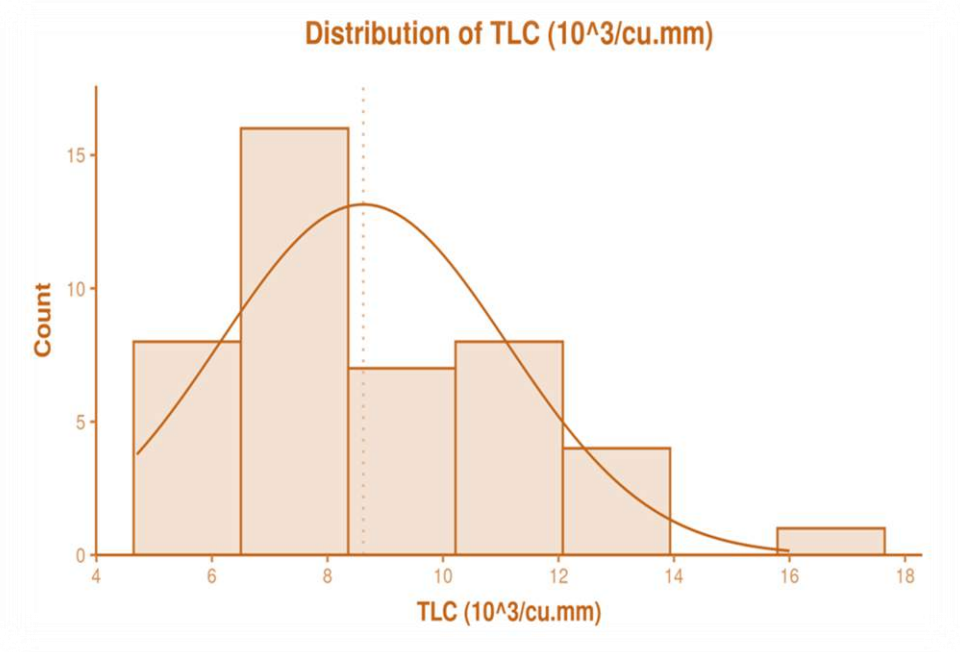


Figure 12: Distribution of the Patients in Terms of TLC

Table 13: Distribution of the Patients in Terms of Anti-tTG Levels (n=44)

S. Anti- tTG (U/ml)*	No. of cases	Percentage
< 100	0	-
100-200	20	45.5%
> 200	24	54.5%

The variable anti-tTG Levels was not normally distributed (Shapiro-Wilk Test: p = <0.001).

As shown in the table, 20 children had anti-tTG value ranging between 100 to 200 U/ml and 24 children had value >200 U/ml. The mean (SD) of anti-tTG Levels was 225.61 (81.14). The anti-tTG Levels ranged from 100 - 360. In this study, all the cases had a raised anti-tTG levels.

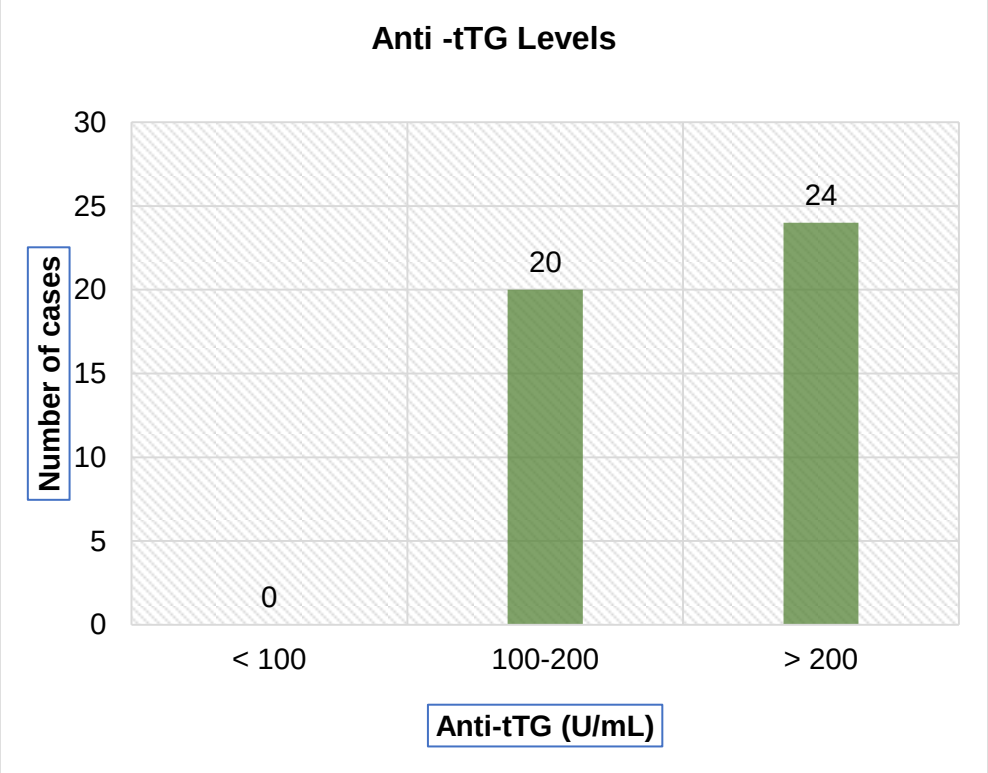


Figure 13: Distribution of the Patients in Terms of Anti-tTG Levels

Table 14: Distribution of the Patients in Terms of Anti-EMA(n=44)

Anti-EMA	Frequency	Percentage
1+	8	18.2%
2+	15	34.1%
3+	11	25.0%
4+	10	22.7%
Total	44	100.0%

Anti-endomysium antibodies are diagnostically sensitive and specific for coeliac disease. Interpretation: +1 positivity denotes minimum immunofluorescence of no significance, +2 positivity denotes weak and clinically insignificant positivity, +3 denotes strong positivity but requires clinical correlation and + 4 denotes strong positivity highly suggestive of coeliac disease. In the present study, 18.2% patients had +1 positivity, 34.1% patients had +2 positivity, 25% had +3 positivity and 22.7% patients had +4 positivity for Anti- EMA.

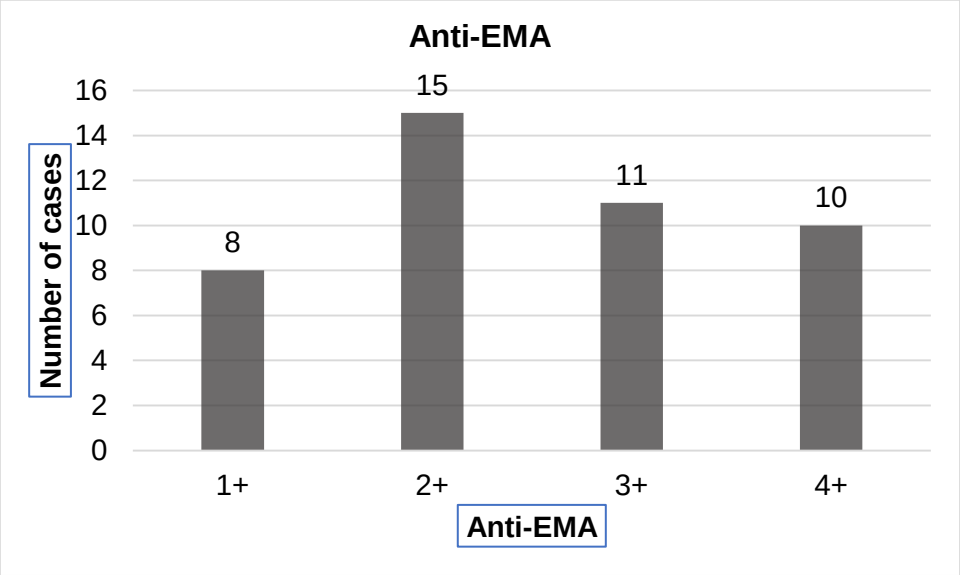


Figure 14: Distribution of the Patients in Terms of Anti-EMA Levels

Table 15: Distribution of the Patients in Terms of HLADQ2 and HLADQ8

	Positive	Negative
HLA DQ2	44 (100%)	0
HLA DQ 8	8 (18.2%)	36 (81.8%)

All patients were positive for at least 1 coeliac-susceptible HLA subtype. All the 44 patients tested positive for HLA-DQ2 and HLA-DQ8 was positive in 18.2% of the patients and negative in 81.8% of the patients.

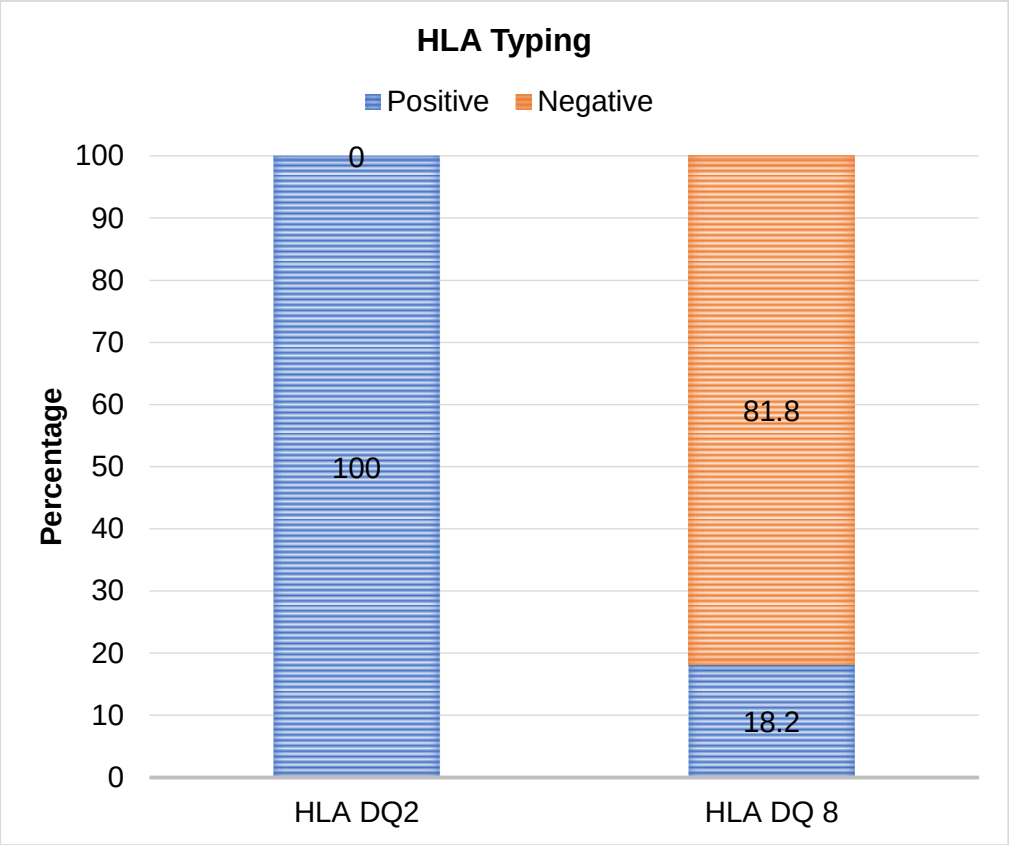


Figure 15: Distribution of the Patients in Terms of HLADQ2 and HLADQ8

Table 16: Distribution of the Patients in Terms of IgA Level (n = 44)

IgA Level(mg/dl)	
Mean (SD)	161.04 (66.60)
Median (IQR)	158 (92.3)
Range	72.1 – 305

The variable IgA Level was not normally distributed (Shapiro-Wilk Test: p = 0.004). The mean (SD) of IgA Level was 161.04 (66.60). The median (IQR) of IgA Level was 158.00 (92.30). The IgA Level ranged from 72.1 - 305.

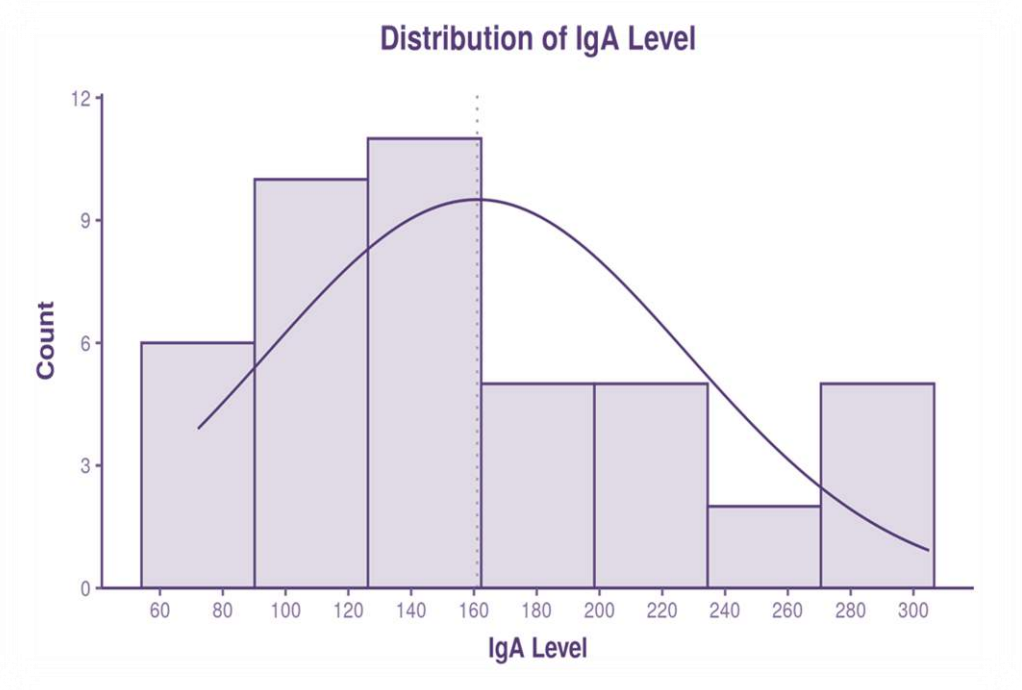


Figure 16: Distribution of the Patients in Terms of IgA Level

Table 17: Distribution of the Patients in Terms of Vitamin D Levels

Vitamin D Levels (ng/ml)	
Mean (SD)	22.57 (8.08)
Median (IQR)	23 (9.21)
Range	6.2 – 46

The variable Vitamin D Levels was normally distributed (Shapiro-Wilk Test: p = 0.386). The mean (SD) of Vitamin D Levels was 22.57 (8.08). The median (IQR) of Vitamin D Levels was 23.00 (9.21). The Vitamin D Levels ranged from 6.2 - 46.

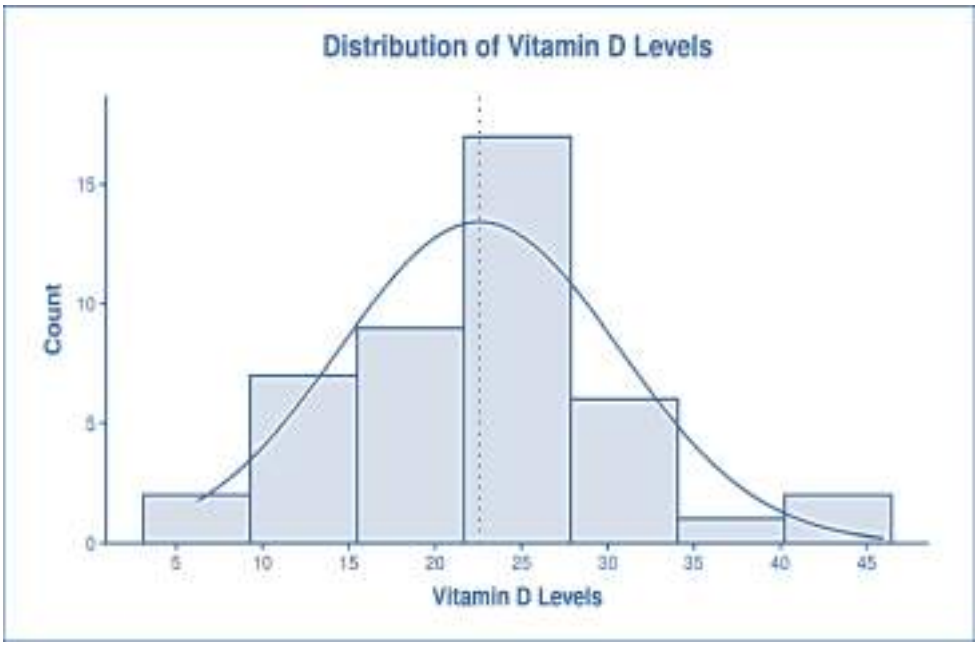


Figure 17: Distribution of the Patients in Terms of Vitamin D Levels

Table 18: Distribution of the Patients in Terms of Modified Marsh Grading (n = 44)

Marsh Grading	Number of cases	Percentage
0	1	2.3%
1	7	15.9%
2	10	22.7%
3A	6	13.6%
3B	11	25.0%
3C	9	20.5%
Total	44	100.0%

Table 18 shows modified Marsh grading of duodenal biopsy in children with coeliac disease. A total of 81.8% of the patients were biopsy positive and rest 18.2% were biopsy negative or inconclusive for coeliac disease. Ten (22.7%) children had duodenal biopsy finding suggestive of modified Marsh grade 2, six (13.6%) children had duodenal biopsy finding suggestive of modified Marsh grade 3 A, eleven (25.0%) children had duodenal biopsy finding suggestive of modified Marsh grade 3 B, nine (20.5%) children had duodenal biopsy finding suggestive of modified Marsh grade 3 C. Endoscopic biopsy was done in all the cases at the time of diagnosis and was not repeated and. Although total villous atrophy was seen in only 9 patients.

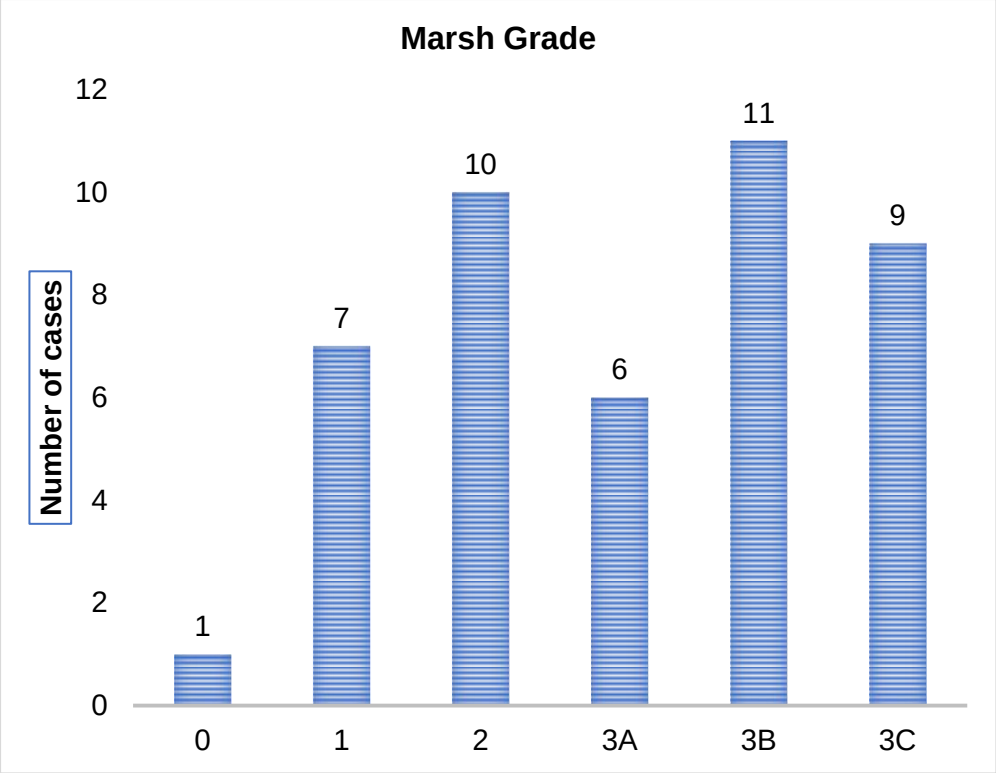


Figure 18: Distribution of the Patients in Terms of Modified Marsh Grading

Table 19: Association between Biopsy and Age Group (n = 44)

Age Group	Biopsy			Fisher's Exact Test	
	Positive	Negative	Total	X^2	P Value
<5 Years	16 (44.4%)	1 (12.5%)	17 (38.6%)	2.817	0.125
≥5 Years	20 (55.6%)	7 (87.5%)	27 (61.4%)		
Total	36 (100.0%)	8 (100.0%)	44 (100.0%)		

Fisher's exact test was used to explore the association between Biopsy results and age group. Sixteen patients were biopsy positive and 1 patient was biopsy negative in less than 5-year age group. Twenty patients were biopsy positive and 7 patients were biopsy negative in more than 5-year age group. There was no significant difference between the various groups in terms of distribution of Age Group (X^2 = 2.817, p = 0.125).

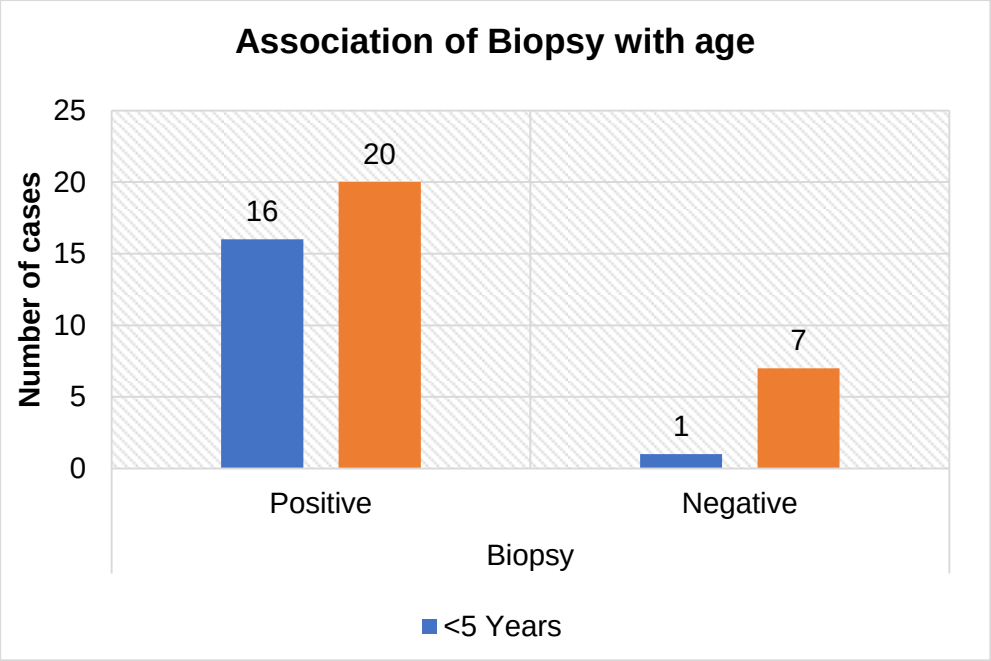


Figure 19: Association between Biopsy and Age Group

Table 20: Association between Biopsy and Gender (n = 44)

Gender	Biopsy			Fisher's Exact Test	
	Positive	Negative	Total	X^2	P Value
Male	24 (66.7%)	5 (62.5%)	29 (65.9%)	0.051	1.000
Female	12 (33.3%)	3 (37.5%)	15 (34.1%)		
Total	36 (100.0%)	8 (100.0%)	44 (100.0%)		

A total of 36 patients were biopsy positive out of which 24 were males and 12 were females. Out of the 8 biopsy negative patients, 5 were males and 3 were females. There was no significant difference between the various groups in terms of distribution of gender (X^2 = 0.051, p = 1.000).

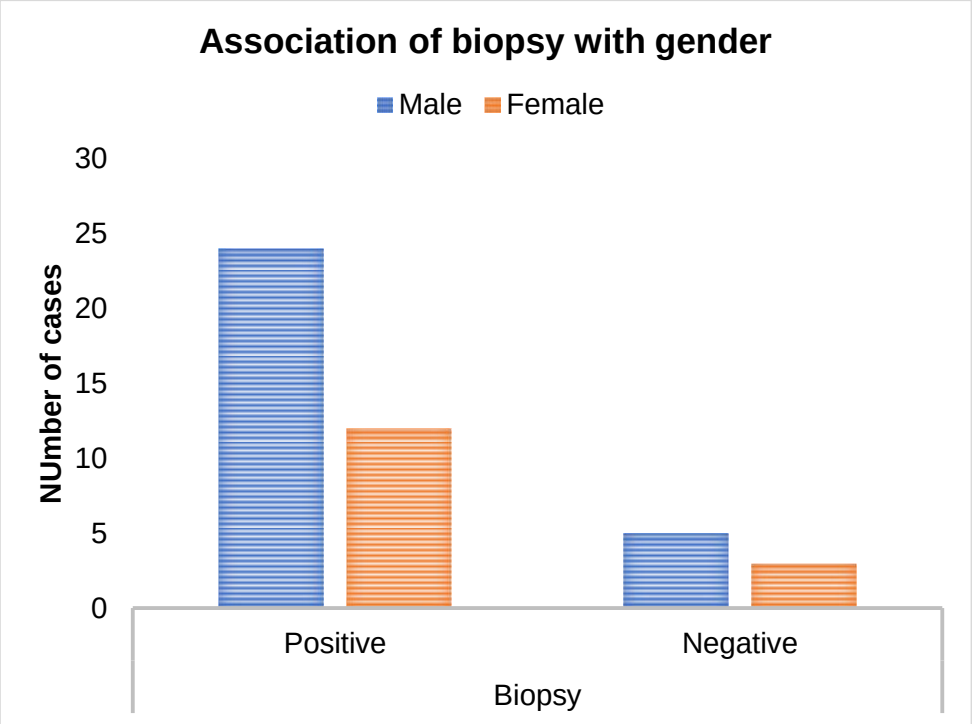


Figure 20: Association between Biopsy and Gender

Table 21: Comparison of the 2 Subgroups of the Variable Biopsy in Terms of Anti-tTG Levels

Anti-tTG Levels	Biopsy		Wilcoxon-Mann-Whitney U Test	
	Positive	Negative	W	p value
Mean (SD)	242.39 (78.52)	150.11 (40.69)	235.500	0.005
Median (IQR)	300 (130.5)	140.65 (52.4)		
Range	100 - 360	110 - 212		

The variable anti-tTG levels was not normally distributed in the 2 subgroups of the variable biopsy. Thus, non-parametric tests (Wilcoxon-Mann-Whitney U Test) were used to make group comparisons.

The mean (SD) anti-tTG levels in the biopsy positive patients was 242.39 (78.52). The mean (SD) anti-tTG levels in the biopsy negative group was 150.11 (40.69). The anti-tTG levels in the biopsy positive patients ranged from 100 – 360 whereas the anti-tTG levels in the biopsy negative group ranged from 110 - 212.

There was a significant difference between the 2 groups in terms of anti-tTG levels (W = 235.500, p = 0.005), with the median anti-tTG Levels being highest in the biopsy positive group.

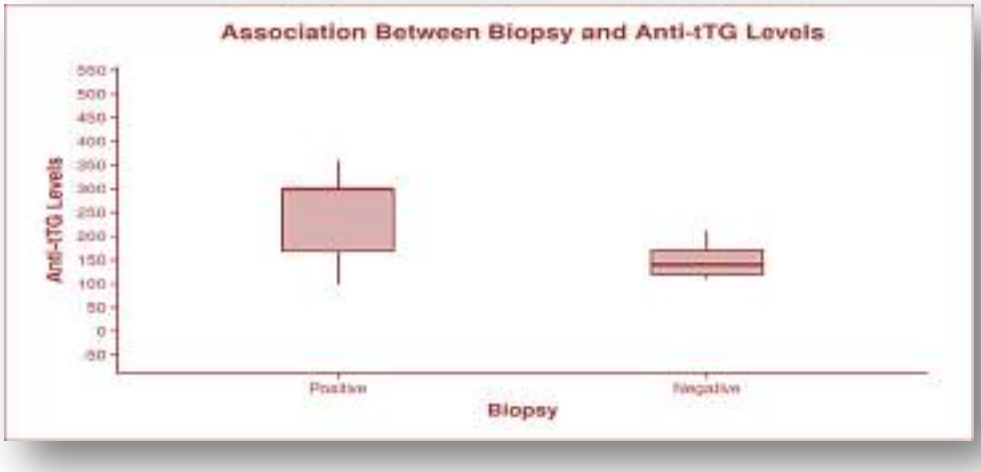


Figure: The Box-and-Whisker plot below depicts the distribution of anti-tTG levels in the 2 groups. The middle horizontal line represents the median anti-tTG levels, the upper and lower bounds of the box represent the 75th and the 25th centile of anti-tTG levels respectively, and the upper and lower extent of the whiskers represent the maximum and the minimum anti-tTG levels in each of the groups.

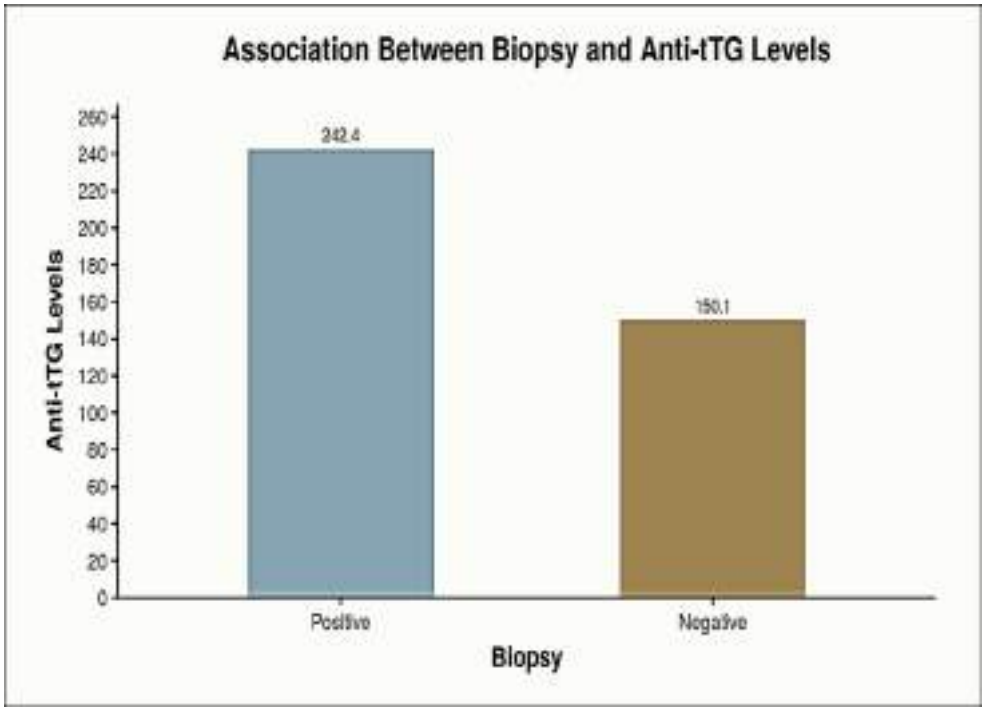


Figure 21: The bar graph below depicts the means of Anti-tTG Levels in the 2 different groups.

Table 22: Association between Biopsy and Anti-EMA

Anti-EMA	Biopsy			Fisher's Exact Test	
	Positive	Negative	Total	X^2	P Value
1+	6 (16.7%)	2 (25.0%)	8 (18.2%)	0.733	0.908
2+	12 (33.3%)	3 (37.5%)	15 (34.1%)		
3+	9 (25.0%)	2 (25.0%)	11 (25.0%)		
4+	9 (25.0%)	1 (12.5%)	10 (22.7%)		
Total	36(100.0%)	8 (100.0%)	44(100.0%)		

In the biopsy positive group, 16.7% of the patients had 1+ anti-EMA positivity, 33.3% of the patients had 2+ anti-EMA positivity, 25% patients had 3+ anti-EMA positivity and rest 25% had 4+ anti-EMA status. In the biopsy negative group, 25% patients had 1+ positivity, 34.2% patients were 2+ positive, 25% patients had 3+ anti-EMA positivity and rest 22.7 % patients had 4+ anti- EMA positivity. There was no significant difference between the various groups in terms of distribution of anti-EMA (X^2 = 0.733, p = 0.908).

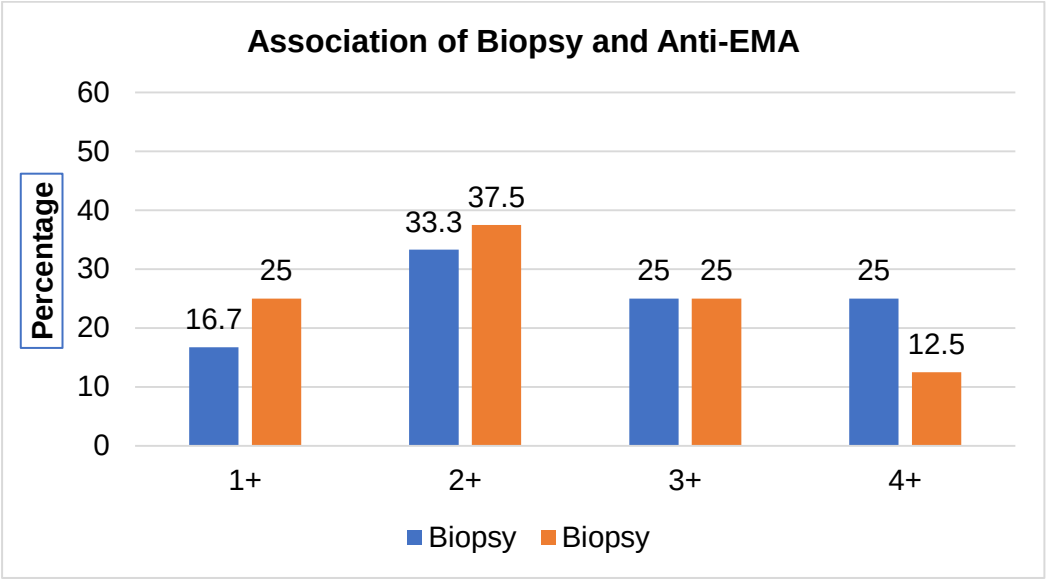


Figure 22: Association between Biopsy and Anti-EMA

Table 23: Comparison of the 6 Subgroups of the Variable Marsh Grading in Terms of Anti-tTG Levels (n = 44)

Anti-tTG Levels	Marsh Grading						Kruskal Wallis Test	
	0	1	2	3A	3B	3C	X^2	p value
Mean (SD)	123.30 (NA)	153.94 (42.36)	218.10 (80.26)	223.00 (87.91)	241.82 (81.70)	283.00 (60.63)	12.553	0.028
Median (IQR)	123.3 (0)	158 (65.8)	225 (123.5)	192 (109)	300 (145)	300 (0)		
Range	123.3 - 123.3	110 - 212	100 - 300	134 - 360	114 - 300	147- 360		

The variable anti-tTG levels was not normally distributed in the 6 subgroups of the variable Marsh Grading. Thus, non-parametric tests (Kruskal Wallis Test) were used to make group comparisons.

The mean anti-tTG levels in the Marsh grade 0 was 123.30. The mean (SD) of anti-tTG levels in the Marsh grade 1 was 153.94 (42.36) whereas in grade 2 was 218.10 (80.26). The mean (SD) of anti-tTG levels in the Marsh grade 3A was 223.00 (87.91) as compared to 241.82 (81.70) in grade 3B. The mean anti-tTG levels were highest in patients with Marsh grade 3C on biopsy with a value of 283(60.63).

There was a significant difference between the 6 groups in terms of anti-tTG Levels (X^2 = 12.553, p = 0.028), with the mean anti-tTG Levels being highest in the Marsh Grading: 3C group.

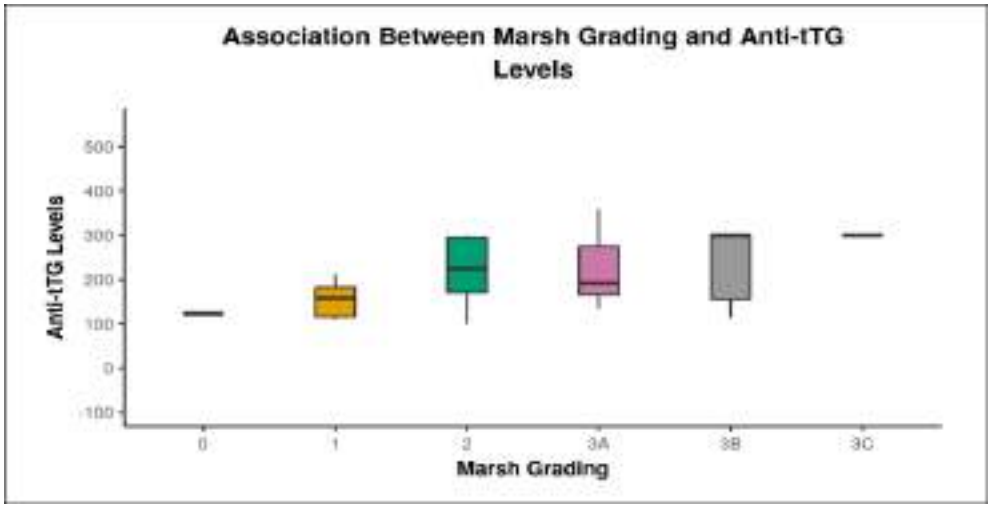


Figure 23: Comparison of the 6 Subgroups of the Variable Marsh Grading in Terms of Anti-tTG Levels

The Box-and-Whisker plot depicts the distribution of Anti-tTG Levels in the 6 groups. The middle horizontal line represents the median Anti-tTG Levels, the upper and lower bounds of the box represent the 75th and the 25th centile of Anti-tTG Levels respectively, and the upper and lower extent of the whiskers represent the maximum and the minimum Anti-tTG Levels in each of the groups.

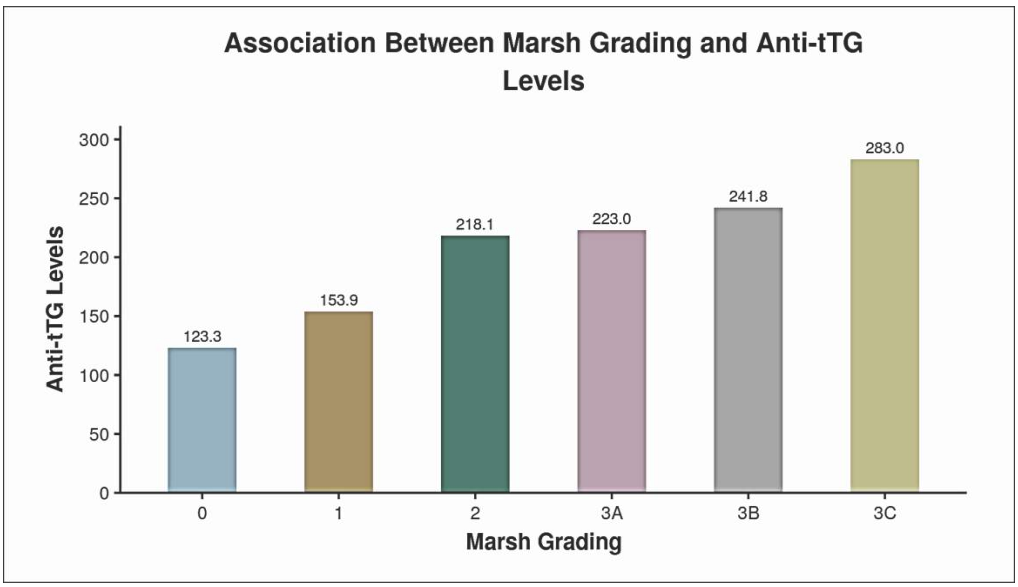


Figure 24: The bar graph below depicts the means of Anti-tTG Levels in the 6 different groups.

Table 24: Association between Marsh Grading and Anti-EMA (n = 44)

Anti-EMA	Marsh Grading							Fisher's Exact Test	
	0	1	2	3A	3B	3C	Total	X^2	P Value
1+	1 (100.0%)	1 (14.3%)	3 (30.0%)	2 (33.3%)	0 (0.0%)	1 (11.1%)	8 (18.2%)	22.722	0.117
2+	0 (0.0%)	3 (42.9%)	4 (40.0%)	3 (50.0%)	4 (36.4%)	1 (11.1%)	15 (34.1%)		
3+	0 (0.0%)	2 (28.6%)	1 (10.0%)	0 (0.0%)	2 (18.2%)	6 (66.7%)	11 (25.0%)		
4+	0 (0.0%)	1 (14.3%)	2 (20.0%)	1 (16.7%)	5 (45.5%)	1 (11.1%)	10 (22.7%)		
Total	1 (100.0%)	7 (100.0%)	10 (100.0%)	6 (100.0%)	11 (100.0%)	9 (100.0%)	44 (100.0%)		

Fisher's exact test was used to explore the association between Marsh grading and Anti-EMA. Patient with Marsh grade 0 had +1 anti-EMA positivity. Three patients with Marsh grade 1 had +2 positivity and 2 patients had +3 anti-EMA positivity. Only 1 patient in Marsh grade 3A group had strong positivity for anti-EMA, rest of the 5 patients had weak positivity. In patients with Marsh grade 3B, 5 patients had +4 positivity, 2 patients had +3 positivity and 4 patients had +2 positivity. In patients with Marsh grade 3C, 6 patients had +3 positivity and only one patient had +4 anti-EMA positivity.

There was no significant difference between the various groups in terms of distribution of Anti-EMA (X^2 = 22.722, p = 0.117).

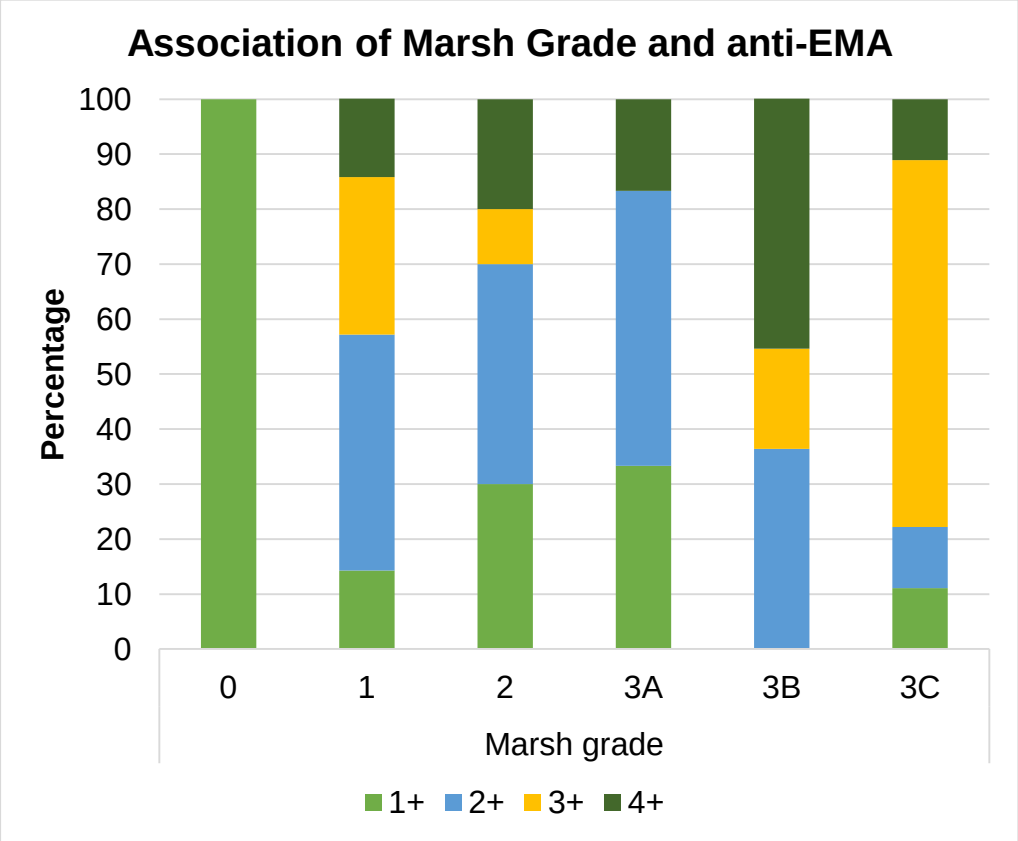


Figure 25: Association between Marsh Grading and Anti-EMA (n = 44)

Table 25: Distribution of the Patients in Terms of ESPGHAN Score (n = 44)

ESPGHAN Score	
Mean (SD)	6.23 (0.80)
Median (IQR)	6 (1)
Range	5 – 7

The variable ESPGHAN score was not normally distributed (Shapiro-Wilk Test: p = <0.001). The mean (SD) of ESPGHAN score was 6.23 (0.80). The median (IQR) of ESPGHAN score was 6.00 (1.00). The ESPGHAN score ranged from 5 - 7.

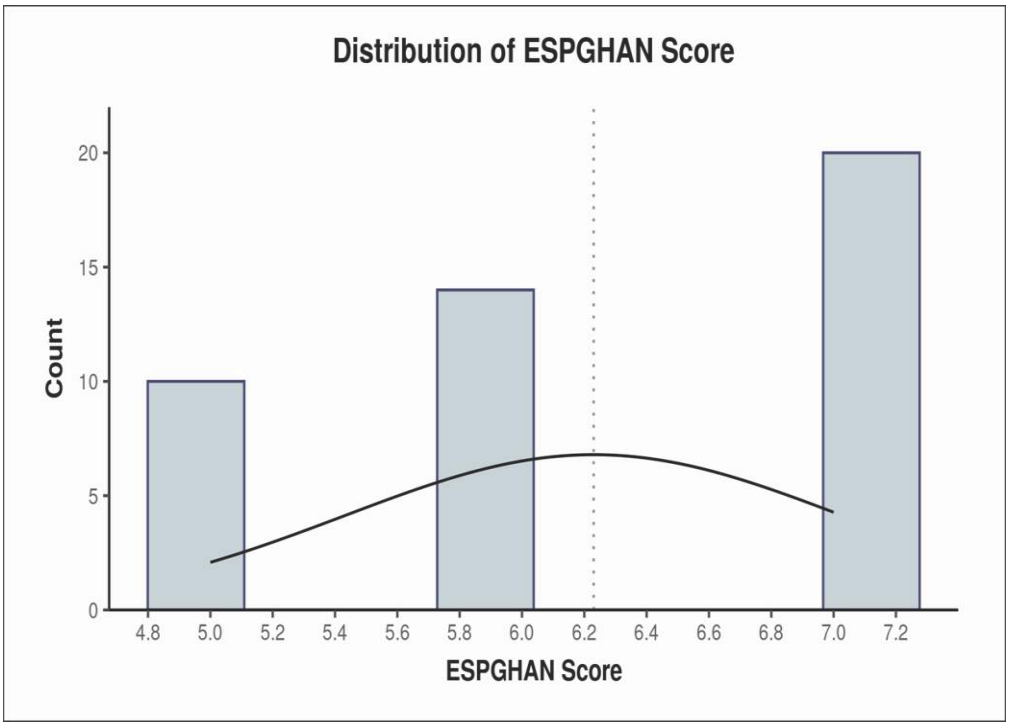


Figure 26: Distribution of the Patients in Terms of ESPGHAN Score (n = 44)

Table 26: Comparison of the Age Groups in Terms of ESPGHAN Score (n = 44)

ESPGHAN Score	Age Group		Wilcoxon-Mann-Whitney U Test	
	<5 Years	≥5 Years	W	p value
Mean (SD)	6.35 (0.79)	6.15 (0.82)	261.500	0.414
Median (IQR)	7 (1)	6 (1.5)		
Range	5 - 7	5 - 7		

The mean (SD) of ESPGHAN score in the age group <5 years was 6.35 (0.79) and in the age group ≥5 years was 6.15 (0.82). There was no significant difference between the groups in terms of ESPGHAN Score (W = 261.500, p = 0.414).

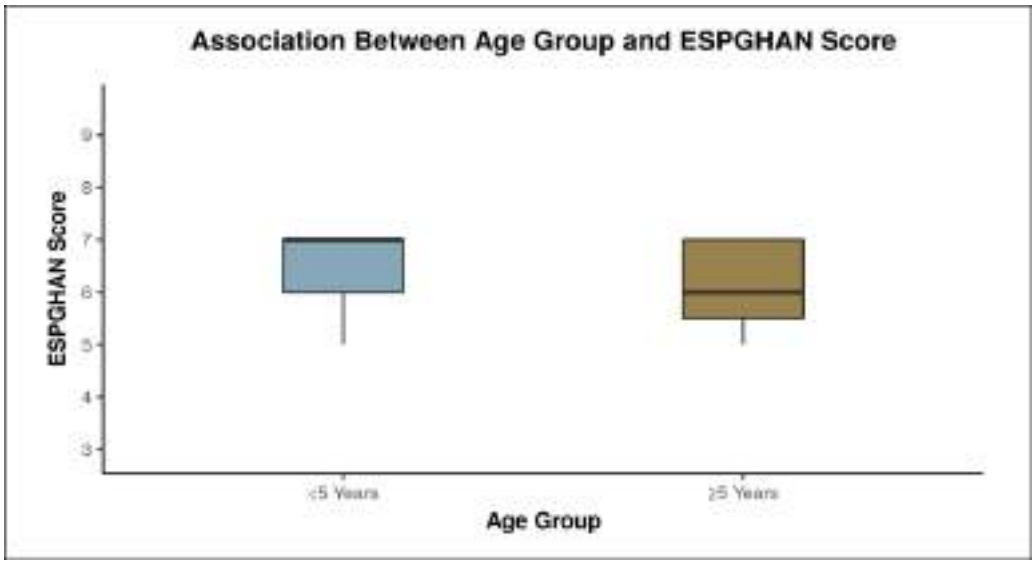


Figure 27: Comparison of the Age Groups in Terms of ESPGHAN Score

The Box-and-Whisker plot depicts the distribution of ESPGHAN Score in the 2 groups. The middle horizontal line represents the median ESPGHAN Score, the upper and lower bounds of the box represent the 75th and the 25th centile of ESPGHAN Score respectively, and the upper and lower extent of the whiskers represent the maximum and the minimum ESPGHAN Score in each of the groups.

Table 27: Comparison of the 2 Subgroups of the Variable Gender in Terms of ESPGHAN Score (n = 44)

ESPGHAN Score	Gender		Wilcoxon-Mann-Whitney U Test	
	Male	Female	W	p value
Mean (SD)	6.28 (0.84)	6.13 (0.74)	243.500	0.497
Median (IQR)	7 (1)	6 (1)		
Range	5 - 7	5 - 7		

The mean (SD) of ESPGHAN score in the male group was 6.28 (0.84). The mean (SD) of ESPGHAN score in the female group was 6.13 (0.74).

There was no significant difference between the groups in terms of ESPGHAN Score (W = 243.500, p = 0.497).

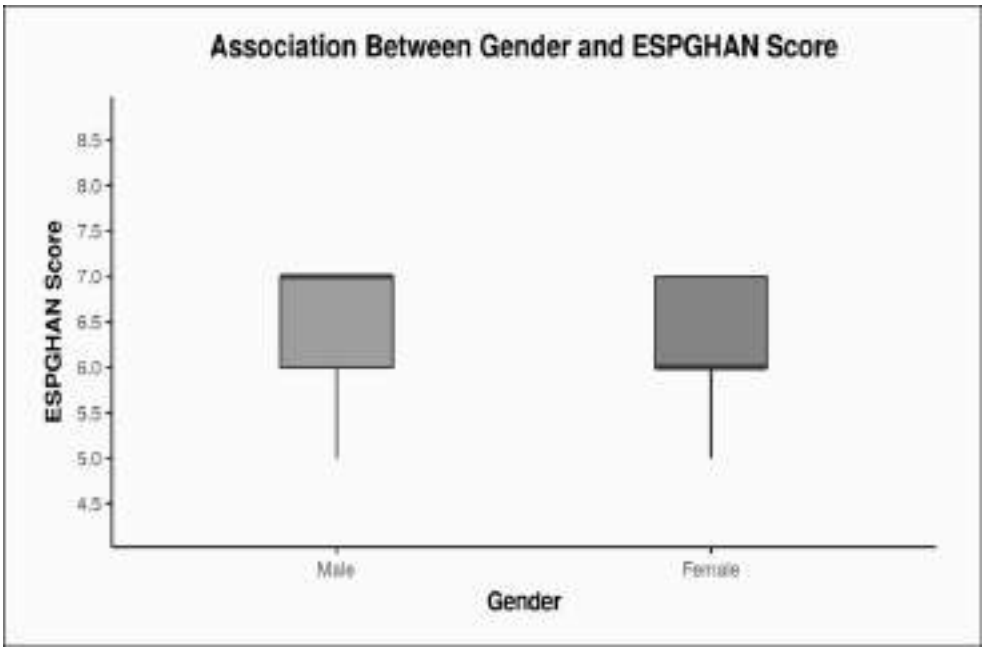


Figure 28: Association between Gender in Terms of ESPGHAN Score

Table 28: Correlation between Anti-tTG Levels and ESPGHAN Score (n = 44)

Correlation	Spearman Correlation Coefficient	P Value
Anti-tTG Levels vs ESPGHAN Score	0.450	0.002

The above scatterplot depicts the correlation between Anti-tTG Levels and ESPGHAN Score. Individual points represent individual cases. The blue trendline represents the general trend of correlation between the two variables. The shaded grey area represents the 95% confidence interval of this trendline. distributed.

There was a moderate positive correlation between Anti-tTG Levels and ESPGHAN Score, and this correlation was statistically significant (rho = 0.45, p = 0.002).

Table 29: Comparison of the 4 Subgroups of the Variable Anti-EMA in Terms of ESPGHAN Score (n = 44)

ESPGHAN Score	Anti-EMA				Kruskal Wallis Test	
	1+	2+	3+	4+	X^2	p value
Mean (SD)	5.75 (0.71)	6.20 (0.77)	6.55 (0.82)	6.30 (0.82)	5.255	0.154
Median (IQR)	6 (1)	6 (1)	7 (0.5)	6.5 (1)		
Range	5 - 7	5 - 7	5 - 7	5 - 7		

The mean (SD) ESPGHAN score in the anti-EMA: 1+ group was 5.75 (0.71) as compared to 6.20 (0.77) in patients with 2+ Anti-EMA. The mean (SD) of ESPGHAN score in the Anti-EMA 3+ group was 6.55 (0.82) and in the Anti-EMA: 4+ group was 6.30 (0.82). There was no significant difference between the groups in terms of ESPGHAN Score (X^2 = 5.255, p = 0.154).

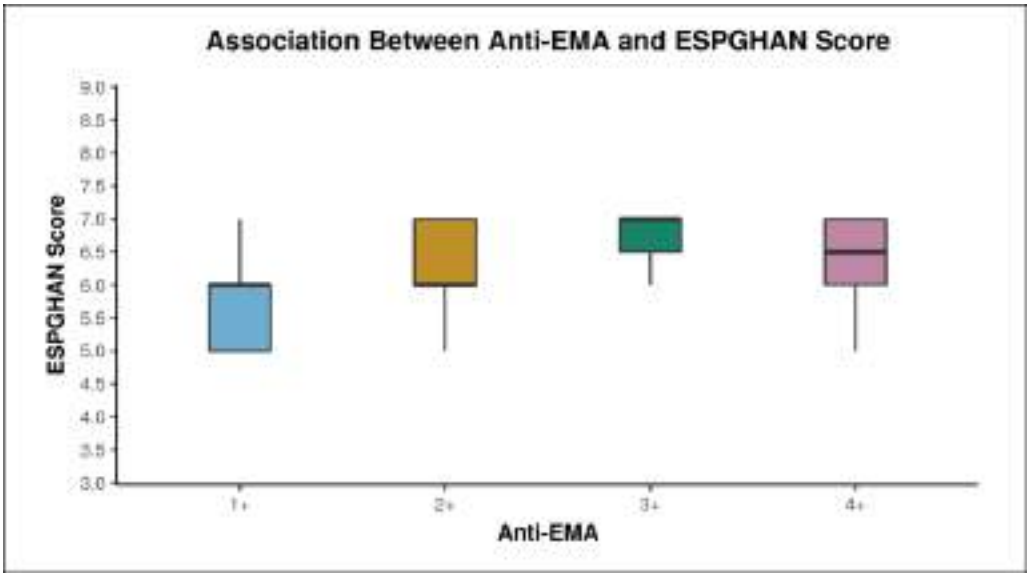


Figure 29: Association between Anti-EMA in Terms of ESPGHAN Score

Table 30: Performance of Study Parameters for Predicting Biopsy: Positive vs Negative

Description of Variables

Variable	Category(s) Suggesting Outcome Present	Category(s) Suggesting Outcome Absent	Total Positives	True Positives	True Negatives	False Positives	False Negatives
Biopsy	Positive	Negative	36 (81.8%)	-	-	-	-
Anti-tTG Levels (Cutoff: 230 by ROC)	>=230	<230	22 (50.0%)	22 (50%)	8 (18%)	0 (0%)	14 (32%)
Anti-EMA	2+, 3+, 4+	1+	36 (81.8%)	30 (68%)	2 (5%)	6 (14%)	6 (14%)
HLADQ8	Positive	Negative	8 (18.2%)	8 (18%)	8 (18%)	0 (0%)	28 (64%)
IgA Level (Cutoff: 187 by ROC)	>=187	<187	15 (34.1%)	15 (34%)	8 (18%)	0 (0%)	21 (48%)

Primary Diagnostic Parameters

Variable	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
Anti-tTG Levels (Cut off: 230 by ROC)	61.1% (43-77)	100.0% (63-100)	100.0% (85-100)	36.4% (17-59)	68.2% (52-81)
Anti-EMA	83.3% (67-94)	25.0% (3-65)	83.3% (67-94)	25.0% (3-65)	72.7% (57-85)
HLADQ8	22.2% (10-39)	100.0% (63-100)	100.0% (63-100)	22.2% (10-39)	36.4% (22-52)
IgA Level (Cut off: 187 by ROC)	41.7% (26-59)	100.0% (63-100)	100.0% (78-100)	27.6% (13-47)	52.3% (37-68)

Table 31: Efficiency of triple test in patients suspected of having coeliac disease

	Biopsy positive N=36	Biopsy negative N= 8	
Triple test positive N=36	30	6	PPV= 30/36 =83.33%
Triple test negative N= 8	6	2	NPV= 2/8 =25%
	Sensitivity= 30/36 = 83.33%	Specificity= 2/8 = 25%	

PPV- positive predictive value; NPV- negative predictive value

In this study, 36 patients were triple test positive. All the cases had a raised Anti-tTG levels and were positive for at least 1 coeliac-susceptible HLA subtype. Six patients had +1 Anti-EMA positivity suggesting minimum immunofluorescence of no significance. A total of 81.8% (36) of the patients were biopsy positive and rest 18.2% (8) were biopsy negative or inconclusive for coeliac disease. Based on these results, specificity for the triple test was 25% and sensitivity was 83.3%, while negative predictive value (NPV) was 25% and positive predictive value (PPV) was 83.3%.

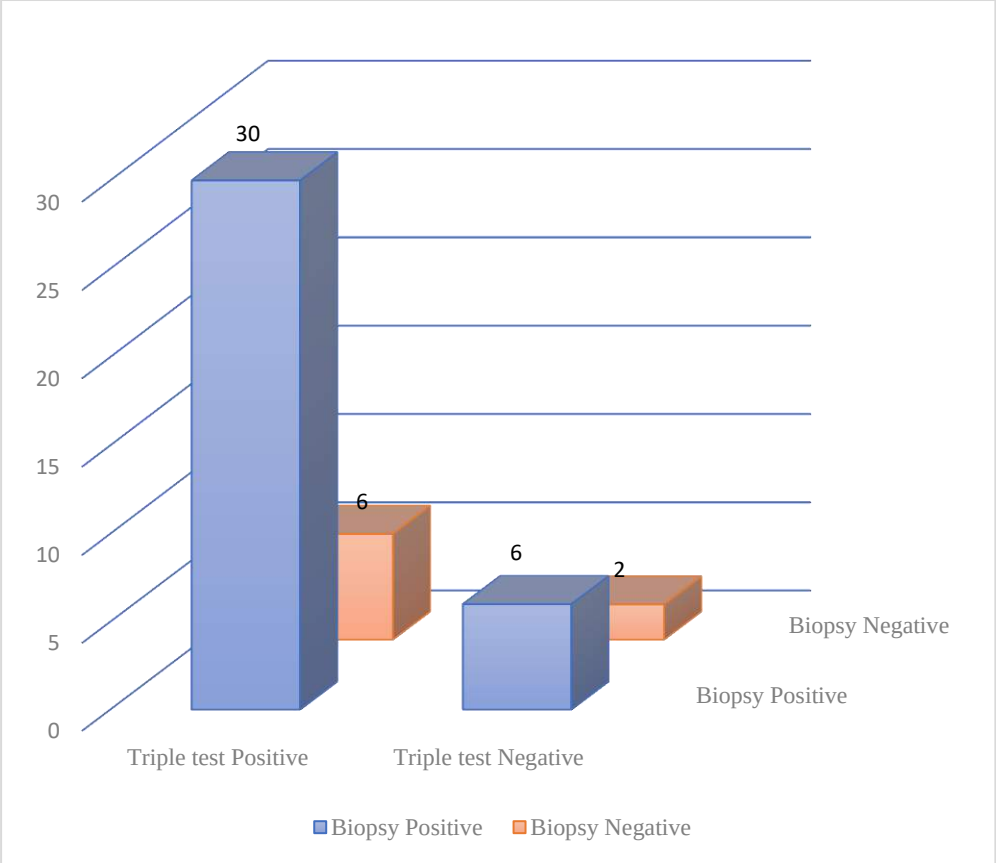


Figure 30: Efficiency of triple test in patients suspected of having coeliac disease

DISCUSSION

Coeliac disease (CD) is an immune-mediated enteropathy triggered by the ingestion of gluten in genetically susceptible individuals.[41] Although CD can present at any age, including the elderly, typical cases often manifest in early childhood. CD may present with a large variety of nonspecific signs and symptoms. It is important to diagnose CD not only in children with obvious gastrointestinal symptoms but also in children with a less clear clinical picture because the disease may have negative health consequences. The availability of serological tests with high accuracy and other diagnostic tests allows a firm diagnosis to be made.

In January 2012, the ESPGHAN published a guideline on diagnosis of CD in children.[39] The guideline recommends that, for symptomatic patients with strongly positive coeliac serology (anti-tTG >10 times the upper limit of normal and positive EMA on separate blood test) and consistent human leukocyte antigen typing (HLADQ2 and/or -DQ8), the diagnosis of CD may be made without the need for small intestinal biopsy.

This present prospective observational study was conducted in G.I. clinic of Paediatric O.P.D. in Dayanand Medical College & Hospital, Ludhiana, over a period of one and a half year and was aimed to evaluate triple test (HLA, Anti-tTG, Anti-EMA) as a diagnostic criterion for CD.

DEMOGRAPHIC AND CLINICAL PROFILE OF CHILDREN WITH COELIAC DISEASE

Age Distribution: The mean age of children included in this study was 7.02 ± 4.07 years with a range of 1.5 to 15 years. Maximum number of children belonged to the age group 3-5 years (34.2%).

In a study conducted by Bishop et al[38] to evaluate the new ESPGHAN guidelines in children with age range from 20 months to 15 years 2 months (median-7 years 3 months). The mean age at diagnosis was comparable to the other studies from India. A study conducted by Pooni et al[42] in north Indian children with CD, the mean

age at diagnosis was 8.92 years (range- 2 to 18 years). Poddar et al.[43] in their study found that age range at presentation was 6.8 to 9.2 years, similarly, Mohindra et al[44] in their study showed that mean age at diagnosis in children with coeliac disease was 8.3 years (range 3 to 14 years).

A study done by Rashid et al[45] in Canadian children with CD, showed the mean age at the time of diagnosis was 9.1 ± 4.1 years (range 1 to 15 years).

Gender Distribution: In our study, most of the patients were males i.e. 29 (66%) and 15 (34%) were females as shown. Male to female ratio was 1.93:1. Among females, maximum cases were in age group of 3 to 5 years i.e. 5/15 (33.3%), followed by 6 to 8 years group i.e. 4/15 (26.7%) and 3 patients in 12 to 14 years age group. There was no statistically significant difference in the gender distribution among various age groups.

In the study conducted by Pooni et al[42] on CD in the north Indian children showed a slight female predominance, female to male ratio was 1.03:1. In a study from north India by Sood et al [46] showed a female to male ratio of 1.3:1 in CD patients. Another study done by Laass et al[47] showed male to female ratio of 1.05:1. In a study done by Bishop et al[38] also had female predominance in their study with 63% of the participants being females. CD is an autoimmune disease and is more common in females, male predominance in current study could be explained by the fact that it was a cross-sectional study conducted on follow up cases, and there is inherent gender bias for males in developing countries.

Socio-economic Status: In our study, majority of the patients belonged to middle class socio-economic group, i.e. 63.6% in upper middle-class group and 31.8% in lower middle-class group. Lower class and upper class had only 2.3% of children each.

Studies on relation between socio-economic status and CD prevalence have shown mixed results. A Study done by Whyte et al[48] studied environmental and genetic factors associated with CD in 232 patients and found out that CD was more common in high socio-economic

groups in their study. In a study conducted in Saudi Arabia by Aljebreen et al[49] on sero- prevalence of coeliac disease showed that the majority of the study population was classified as lower middle class (82.7%).

Although there is no scientific basis of association of socio-economic status and coeliac disease prevalence, high prevalence of coeliac disease in middle class group in current study could be explained by the fact that middle and upper class people have better access to medical facilities in developing countries like India.

Clinical Spectrum: In our study, pain abdomen was the most common presenting complaint present in 90.9% of the patients followed by constipation and poor weight gain. Loose stools were presenting complaint in 25% of the patients. As the age of children increase, the clinical symptoms become more subtle.[41]

In a study done by Bishop et al[38] the most common symptom was abdominal pain followed by loose stools and constipation.

In a study conducted by Geng et al[50] to analyze the clinical features of coeliac disease in different ethnic groups showed that the proportions of weight loss, growth retardation, iron deficiency anemia and dermatitis herpetiformis in Asian group were significantly higher than that in Caucasian group ($p<0.05$).

In the study conducted in Sicily, Italy by Magazzú G et al[51] in 4 gastro-enterology centers showed that growth failure and chronic diarrhea were the most common symptoms in patients with coeliac disease, but a diminishing trend for chronic diarrhea was observed when symptoms were distributed by year of diagnosis.

ESPGHAN guidelines 2020 also recommended considering diagnosis of CD if these intestinal symptoms were more than general population.

Conditions associated with CD: Various autoimmune conditions have been associated with CD since very beginning. Children with CD were screened for other associated autoimmune and systemic conditions at the time of diagnosis. In our study, 90.9% children in the study had iron deficiency anaemia. Among 44 children 7 (15.9%) had some associated allergic disorder, 6 children (13.6%) had bronchial

asthma, 32 children (72.7%) had associated Vitamin D deficiency. Type-1 DM was diagnosed in 1 child. Ventricular septal defect was also diagnosed in 1 child. Only 1 child in this study was hypothyroid.

In a study done by Sanseviero et al, [52]iron deficiency anemia in newly diagnosed CD children confirmed that iron deficiency anemia represented a frequent finding at the diagnosis of CD. In another study conducted by Repo et al[53] concluded that development of anemia and iron deficiency in coeliac disease is a continuum and may already be present in children with normal villous morphology, advocating an early diagnosis and possible dietary treatment of these patients.

Family history of CD: Coeliac disease has a proven genetic predisposition. In our study, 4 patients (9.1%) with coeliac disease had positive family history of coeliac disease. Among these 3 were first degree relatives, 1 was second degree relative. But majority of the children, i.e. 90.9%, did not have history of coeliac disease in their families.

There are many studies showing high prevalence of coeliac disease among family members. In a study from Slovenia conducted by Dolinsek et al.[54] showed that the prevalence of CD

among first-degree relatives was much higher than the prevalence of the disease in the general population. Their study showed prevalence of coeliac disease among first degree relatives was 5.67%. In another study from Punjab region of Indian subcontinent conducted by Gautam et al.[55] showed that CD is common among siblings of patients with CD in Punjab and may be asymptomatic.

Growth parameters: In children less than 5 years of age, 3/44 (6.8%) children had weight less than 3rd percentile and 5/44 (11.4%) children had height less than 3rd percentile. In children more than 5 years of age, 5/44 (11.4%) children had weight less than 3rd percentile and, 6.8% of the children had height less than 3rd centile. In a study done by Assa et al[56] on anthropometric measures in coeliac disease found out that the adolescent boys with CD were leaner and girls with CD were shorter compared with the general population. In a study done by Chisty et al[57] on nutritional status in coeliac and non-coeliac children

from Rajasthan showed that the non-coeliac children were significantly taller and heavier than coeliac children. In a study by Bardella et al[58], it was revealed that the weight, height and BMI of male coeliac patients and the weight and BMI of female CD patients were significantly lower than the corresponding measurements in control children.

INVESTIGATIONS IN CHILDREN WITH COELIAC DISEASE

Haemoglobin Levels: CD is a common cause of various hematologic disorders, the most common of which is anemia. The anemia of CD is usually due to malabsorption of micronutrients such as iron, folic acid, and vitamin B12. In our study, the mean (SD) of haemoglobin) was 10.64 (1.71). g/dL and the haemoglobin values ranged from 7.4 - 14.5 g/dL.

CD is frequently diagnosed in patients referred for evaluation of anemia. The subclinical CD appears to be a relatively common cause of iron deficiency anaemia (IDA).[59-61] Studies using serologic tests and small-bowel biopsies in patients referred for evaluation of IDA have reported CD in 0% to 8.7% of patients. Two studies have evaluated patients with IDA biopsy-proven CD was reported in 2.6% to 5% of patients.[59-60] Three other studies included patients with anemia other than IDA but the vast majority in all 3 studies suffered from IDA.[61,62,63] Serologic evidence of CD was observed in 2.3% to 10.9% of these anemic patients.

Anti-tTG Levels: The enzyme tissue transglutaminase (tTG) has an important role in the breakdown of proteins in the small intestine. Dietary gliadin triggers the formation of a gliadin peptide–tTG complex in the small intestine. In CD, antibodies to this peptide-tTG complex (anti-tTG antibodies) are formed, leading to mucosal inflammation.

In our study, all the cases had a raised Anti- tTG levels. Twenty children had anti-tTG value ranging between 100 to 200 U/ml and 24 children had value >200 U/ml. The mean anti- tTG levels in the biopsy positive patients was 242.39 ± 78.52 and 150.11 ± 40.69 in biopsy negative group. The difference between the biopsy positive and biopsy

negative groups in terms of anti-tTG levels was statistically significant, with the median anti-tTG levels being highest in the biopsy positive group. There was a significant difference between the 6 groups of Marsh grade in terms of anti-tTG levels, with the mean anti-tTG Levels being highest in the Marsh Grading: 3C group. There was a moderate positive correlation between Anti-tTG Levels and ESPGHAN score, and this correlation was statistically significant.

Our results are in accordance with a study done by Dieterich et al[64] which shows that IgA anti-tTG titers had good correlation with EMA titers, reaching a sensitivity of 98.1% and a specificity of 94.7%. Similarly, Anti-tTG antibodies had a greater than 95% sensitivity and specificity for coeliac disease in a study by Husby et al.[65]

Recent guidelines have proposed that there is a correlation between anti-tTG levels antibody titers and degree of small bowel changes on duodenal biopsy and that duodenal biopsy can be omitted in some patients with high levels of anti-tTG antibody.[66]

Hill et al[67] suggested a cutoff point of a tTG IgA titer >10 times the upper limit of normal, whereas Zanini et al[68] found that titers exceeding 5 times the ULN showed 100% specificity and PPV for duodenal atrophy. Alessio et al[69] reported that all patients with IgA anti tTG IgA titers >7 times the ULN showed histological features of CD. Others found that when the tTG IgA titer is >100 U/ mL, biopsy is not mandatory to confirm the diagnosis, particularly in symptomatic patients.[70] Donaldson et al. showed that all their Paediatric patients with anti-tTG titer ≥ 100 U/mL had Marsh III histopathology of CD.[71]

Trovato et al.[72] evaluated the ESPGHAN biopsy-sparing guideline in symptomatic and asymptomatic coeliac disease and reported no difference histologically between high titer symptomatic and high titer asymptomatic groups as Marsh III was demonstrated in 91% and 92% of these patients, respectively.

Anti-EMA Levels: In our study, 18.2% patients had +1 positivity, 34.1% patients had +2 positivity, 25% had +3 positivity and 22.7% patients had +4 positivity for Anti- EMA. In our study, there was no significant difference between the biopsy positive and biopsy negative

groups in terms of distribution of anti-EMA. There was no significant difference between the 6 Marsh grade groups in terms of distribution of Anti-EMA. There was no significant correlation between Anti-EMA and ESPGHAN Score in our study.

A recent multinational prospective study (ProCeDE)[73] validates this non biopsy approach in children presenting clinical symptoms whenever anti-TG2 levels are >10 × ULN and with positive EMA in a second blood sample, thus supporting the use of EMA as a confirmatory test when CD diagnosis is performed without biopsy.

A study by Tarmure et al. concluded that anti-EMA had a lower sensitivity in patients with Marsh-I and Marsh II lesions.[74]

A recent meta-analysis of diagnostic coeliac antibody testing in children described that, based on enzyme-linked immunosorbent assay testing, the specificity of the tTG ranges between 77.8 and 100%, with the majority of studies reporting specificities >95%. However, a pooled estimate was not performed because of the heterogeneity of the studies included. Multiple medical conditions are known to give rise to a falsely positive tTG, including other autoimmune diseases such as type 1 diabetes mellitus, inflammatory bowel disease, liver disorders, rheumatologic conditions, as well as acute viral infection Therefore, EMA is more specific for CD with a pooled specificity of 98.2%.[75]

HLA-DQ typing in CD: The genetic risk factors for coeliac disease have been well characterized. More than 90% of patients share the major histocompatibility complex II class human leukocyte antigen (HLA) DQ2 haplotype, and most of the remainder, HLA-DQ8.[76] In our study, all patients were positive for at least 1 coeliac-susceptible HLA subtype. All the 44 patients tested positive for HLA-DQ2 and HLA-DQ8 was positive in 18.2% of the patients and negative in 81.8% of the patients. HLA typing has previously been suggested as a cost saving first-line screening step in coeliac disease risk groups, because negative HLA-DQ2 or HLA-DQ8 excludes coeliac disease for life better than serology.

Efficiency of triple test in patients suspected of having CD: In our study, 36 patients were triple test positive. All the cases had a raised Anti-tTG levels and were positive for at least 1 coeliac-susceptible HLA subtype. Six patients had +1 Anti- EMA positivity suggesting minimum immunofluorescence of no significance. A total of 81.8% (36) of the patients were biopsy positive and rest 18.2% (8) were biopsy negative or inconclusive for coeliac disease. Based on these results, specificity for the triple test was 25% and sensitivity was 83.3%, while negative predictive value (NPV) was 25% and positive predictive value (PPV) was 83.3.

A very recent prospective study showed that diagnosis of CD can be reliably performed without a duodenal biopsy in approximately 11% of cases, selected applying the ESPGHAN guidelines in a restricted way, considering as symptomatic only those cases with diarrhoea, weight loss, failure to thrive and iron deficiency anaemia.[77] Guandalini and colleagues expressed concerns about the skipping of duodenal biopsy to confirm the diagnosis of CD.[78] They demonstrated that if the diagnosis of CD is made without the endoscopy, any unexpected disorders of the upper gastrointestinal tract will be missed. They therefore suggest that it is mandatory to closely follow up patients on a gluten free diet and evaluate those with unresolved symptoms.

SUMMARY & CONCLUSIONS

CD is an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals and characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies HLA-DQ2 or HLA-DQ8 haplotypes, and enteropathy.

The duodenal biopsy is the gold standard for the diagnosis of coeliac disease. However, this approach requires considerable investment of time and resources by pathologists.

However, given improvements in the performance of serological testing, the possibility of accurately diagnosing coeliac disease without the need of a biopsy has attracted interest.

The ESPGHAN guideline recommends that, for symptomatic patients with strongly positive coeliac serology (anti-tTG >10 times the upper limit of normal (ULN) and positive EMA on separate blood test) and consistent human leukocyte antigen (HLA) typing (HLA-DQ2 and/or HLA-DQ8), the diagnosis of CD may be made without the need for small intestinal biopsy.

A change in clinical practice (i.e. serologically diagnosing CD) even in context of developing countries should be evidence-based. CD is a diagnosis which needs commitment and adherence to lifelong Gluten-Free Diet (GFD); this is neither economical nor easily available in developing countries. It is, therefore, important to make the initial diagnosis of CD with reasonable certainty and the modified ESPGHAN guidelines may be used in selective symptomatic patients with tTG-titres > 10 x ULN.

This prospective observational study was conducted in the department of Paediatrics at DMC&H, Ludhiana for one year and six months duration i.e. from 1st November 2018 to 30th April 2020 for the symptomatic CD children in age group of 1-18 years who underwent serology for anti-TG2, EMA, HLA serotypes and duodenal biopsy. A total of 54 children enrolled for the study but 10 patients were excluded as 6 did not give consent for duodenal biopsy and 4 were loss to follow

up. So, the final analysis was done for 44 patients using SPSS-22 who completed the required investigations.

Following observation were made:

1. The mean age of the patients in our study was 7.02 ± 4.07 years.
2. 29 (66%) patients were male.
3. 28 (63.6%) patients belonged to upper-middle class of socio-economic status.
4. Pain abdomen was the main presenting symptoms seen in 40 (90.9%) patients followed by constipation and poor weight gain which was present in 25 (56.8%) of the patients.
5. 40 (90.9%) patients had anemia as major associated condition.
6. Family history of CD was positive in 4 (9.1%) patients.
7. The mean haemoglobin was 10.64 ±1.71 g/dL with arrange from 7.4 - 14.5 g/dL followed by vitamin D deficiency in 32 (72.7%) patients
8. The mean vitamin D was 22.57±8.08 ng/ml with a range from 6.2-46.
9. 24 (54.5%) patients had anti-TG2 value >200 U/ml while 20 (45.5%) had value between 100-200 U/ml.
10. All the patients had genetic testing done for HLA-DQ2 and DQ8. 100% of the patients were serologically positive for coeliac-susceptible HLA-DQ2 while HLA-DQ8 was positive in 8 (18.2%) of the patients.
11. 10 (22.7%) patients had strongly positive for EMA serology suggestive of coelic disease while another 11 had significant positive for EMA serology.
12. The mean IgA levels were 161.04 ±66.60 mg/dl with a range from 72.1 - 305.
13. Out of total of 44 patients who underwent duodenal biopsy, 36 (81.8%) of the patients were biopsy positive (Marsh grade 2 or higher) and rest 8 (18.2%) were biopsy negative (Marsh grade 0 or 1).
14. In our study, 94.1 % (16 of 17) children below 5 years the patients were biopsy positive while only 74.1 % (20 out of 27) children above 5 years the patients were biopsy positive.

15. In our study, 82.8 % (24 out of 29) male children were biopsy positive while 80.0 % (12 out of 15) female children were biopsy positive.
16. The mean anti-tTG level in biopsy positive patients was 242.39 ±78.52 U/ml while it was 150.11 ± 40.69 U/ml in biopsy negative patient. This difference was statistically significant.
17. There was no significant difference between the patients who were biopsy positive and their anti-EMA levels
18. A rising anti-tTG levels were observed as as severity of Marsh grade increased.
19. Out of 44 children, 36 (81.8%) patients were triple test positive
20. Based on these results, specificity for the triple test was 25% and sensitivity was 83.3%, while negative predictive value (NPV) was 25% and positive predictive value (PPV) was 83.3%.
21. The mean of ESPGHAN score was 6.23 ± 0.80 with a range from 5 - 7. ESPGHAN score can be used as an additional tool along with triple test serology for diagnosing coeliac disease.

There is significant evidence to follow ESPGHAN guidelines for diagnosis of CD without small intestinal biopsy.

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					SYMPTOMS						ASSOCIATED CONDITIONS											
S.No	NAME	Age (years)	Sex	Address	PAIN ABDOMEN	LOOSE STOOLS	CONSTIPATION	LOSS OF APPETITE	POOR WEIGHT GAIN	VOMITING	ANAEMIA	ASTHMA	HYPOTHYROIDISM	ALLERGIC DISORDER	TYPE 1 DM	VENTRICULAR SEPTAL DEFECT	VIT D DEF	FAMILY HISTORY	SOCIO ECONOMIC STATUS	WEIGHT (INFERENCE)	HEIGHT (INFERENCE)	Head Circumference (< 5yrs) (Actual/Expected/Inference)
1	SK	5	F	Ludhiana	YES	YES	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	UPPER MIDDLE CLASS	3rd to 10th CENTILE	3rd to 10th CENTILE	NA
2	SV	2	M	Moga	YES	NO	YES	YES	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	UPPER MIDDLE CLASS	3rd to 50th CENTILE	3rd to 50th CENTILE	46.5/47.2 (25th to 50th CENTILE)
3	YR	3	M	Ludhiana	YES	YES	NO	YES	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	LOWER MIDDLE CLASS	<3rd CENTILE	< 3rd CENTILE	48/49 (50th CENTILE)
4	GS	10	M	Bhatinda	YES	NO	YES	YES	YES	NO	YES	NO	NO	NO	NO	NO	NO	NO	LOWER MIDDLE CLASS	3rd to 10th CENTILE	3rd to 10th CENTILE	NA
5	AN	6	F	Pathankot	YES	NO	YES	NO	NO	NO	YES	YES	NO	YES	NO	NO	YES	YES	UPPER MIDDLE CLASS	3rd to 10th CENTILE	3rd to 10th CENTILE	NA
6	PK	12	F	Ferozpur	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	LOWER MIDDLE CLASS	10th to 25th CENTILE	10th to 25th CENTILE	NA
7	SR	5	F	Ludhiana	YES	YES	NO	NO	NO	YES	YES	NO	NO	NO	NO	NO	YES	NO	UPPER MIDDLE CLASS	<3rd CENTILE	3rd to 10th CENTILE	NA
8	JD	9	M	Doraha	YES	NO	YES	NO	NO	NO	YES	YES	NO	NO	NO	NO	NO	NO	UPPER MIDDLE CLASS	10th to 25th CENTILE	10th to 25th CENTILE	NA
9	JP	7	M	Nawashehar	YES	YES	NO	YES	NO	NO	YES	YES	NO	NO	NO	NO	YES	NO	UPPER CLASS	10th to 25th CENTILE	10th to 25th CENTILE	NA
10	MS	7	M	Mrkotla	YES	NO	NO	YES	YES	NO	YES	NO	NO	NO	NO	NO	YES	NO	LOWER MIDDLE CLASS	3rd to 10th CENTILE	3rd to 10th CENTILE	NA
11	BH	14	F	Ludhiana	YES	YES	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	YES	NO	UPPER MIDDLE CLASS	10th to 25th CENTILE	10th to 25th CENTILE	NA
12	AK	5	F	Ajnaud	YES	NO	YES	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	LOWER MIDDLE CLASS	10th to 25th CENTILE	10th to 25th CENTILE	NA
13	LA	3	M	Mrkotla	YES	YES	NO	NO	NO	NO	YES	NO	NO	YES	NO	NO	YES	NO	UPPER MIDDLE CLASS	3rd to 50th CENTILE	3rd to 50th CENTILE	47.5/48.5 (25th to 50th CENTILE)
14	AL	9	F	ludhiana	YES	YES	NO	NO	YES	YES	YES	NO	NO	YES	NO	NO	NO	NO	UPPER MIDDLE CLASS	3rd to 10th CENTILE	10th to 25th CENTILE	NA
15	GK	7	F	Nawashehar	YES	NO	YES	YES	YES	NO	YES	YES	NO	NO	NO	NO	NO	YES	UPPER MIDDLE CLASS	3rd to 10th CENTILE	10th to 25th CENTILE	NA
16	SS	5	M	Sunam	YES	YES	NO	NO	NO	YES	YES	NO	NO	YES	NO	NO	YES	NO	LOWER MIDDLE CLASS	3rd to 10th CENTILE	3rd to 10th CENTILE	NA
17	SL	7	F	Barnala	YES	NO	NO	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	UPPER MIDDLE CLASS	10th to 25th CENTILE	10th to 25th CENTILE	NA
18	JK	4	F	Mansa	YES	NO	YES	YES	YES	NO	YES	NO	NO	NO	NO	NO	YES	NO	UPPER MIDDLE CLASS	3rd to 50th CENTILE	3rd CENTILE	46.5/48cm (3rd to 50th CENTILE)
19	AP	12	F	Phillaur	YES	NO	YES	YES	YES	NO	YES	NO	NO	NO	NO	NO	YES	NO	UPPER MIDDLE CLASS	<3rd CENTILE	3rd to 10th CENTILE	NA
20	GS	4	M	Gurdaspur	NO	NO	YES	YES	YES	NO	YES	NO	NO	NO	NO	NO	YES	NO	LOWER MIDDLE CLASS	3rd CENTILE	3rd to 50th CENTILE	49/50 (3rd to 50th CENTILE)
21	PR	12	M	Pathankot	YES	NO	NO	YES	YES	NO	YES	NO	NO	NO	NO	NO	YES	NO	UPPER MIDDLE CLASS	3rd to 10th CENTILE	3rd to 10th cnetile	NA
22	HD	14	M	gurdaspur	YES	NO	NO	YES	YES	NO	YES	NO	NO	NO	NO	NO	YES	NO	UPPER MIDDLE CLASS	10th CENTILE	10th CENTILE	NA
23	HS	3	M	Mrkotla	YES	NO	YES	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	YES	LOWER MIDDLE CLASS	3rd to 50 th CENTILE	3rd to 50th CENTILE	48.5/49 (50th CENTILE)
24	GS	3	M	Ludhiana	YES	NO	YES	NO	YES	YES	YES	NO	NO	NO	NO	YES	YES	NO	UPPER MIDDLE CLASS	3rd CENTILE	< 3rd CENTILE	47.5/49 (3rd to 50th CENTILE)
25	KK	4.5	M	Ludhiana	NO	YES	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	YES	NO	UPPER MIDDLE CLASS	3rd to 50th CENTILE	3rd to 50th CENTILE	50/50 (50th CENTILE)
26	HS	15	M	Mansa	YES	NO	YES	YES	YES	NO	YES	NO	NO	NO	NO	NO	YES	NO	LOWER MIDDLE CLASS	< 3rd CENTILE	< 3rd CENTILE	NA
27	AN	10	F	Ludhiana	YES	NO	YES	NO	YES	NO	NO	YES	NO	YES	NO	NO	YES	YES	LOWER CLASS	3rd o 10th CENTILE	3rd to 10CENTILE	NA
28	GS	6	M	Khanna	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	NO	LOWER MIDDLE CLASS	3rd to 10th CENTILE	10th to 25th CENTILE	NA
29	PV	3	F	Jalandhar	YES	YES	NO	YES	NO	NO	YES	NO	NO	NO	NO	NO	YES	NO	UPPER MIDDLE CLASS	3rd to 50th CENTILE	3rd to 50th CENTILE	48/48.5 (3rd to 50th CENTILE)
30	MS	8	M	Moga	YES	NO	YES	YES	YES	NO	YES	NO	NO	YES	NO	NO	YES	NO	UPPER MIDDLE CLASS	3rd to 10th CENTILE	3rd to 10th CENTILE	NA
31	AD	12	M	Moga	YES	NO	YES	NO	YES	NO	YES	NO	NO	NO	NO	NO	YES	NO	UPPER MIDDLE CLASS	3rd to 10th CENTILE	<3rd CENTILE	NA
32	RV	2	M	Moga	YES	YES	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	YES	NO	UPPER MIDDLE CLASS	3rd to 50th CENTILE	<3rd CENTILE	48/48 (50th CENTILE)
33	AP	6	F	Samrala	NO	NO	NO	YES	YES	NO	YES	NO	NO	NO	NO	NO	YES	NO	UPPER MIDDLE CLASS	3rd to 10th CENTILE	10th to 25th CENTILE	NA
34	AN	2	F	Moga	NO	YES	NO	NO	YES	YES	YES	NO	NO	NO	NO	NO	YES	NO	UPPER MIDDLE CLASS	<3rd CENTILE	< 3rd CENTILE	46/47 (3rd to 50th CENTILE)
35	AJ	10	M	Ludhiana	YES	NO	NO	NO	YES	NO	YES	NO	NO	NO	NO	NO	YES	NO	UPPER MIDDLE CLASS	10th CENTILE	3rd to 10th CENTILE	NA
36	GS	4	M	Amritsar	YES	NO	YES	YES	YES	NO	YES	NO	NO	NO	NO	NO	NO	NO	UPPER MIDDLE CLASS	3rd to 50th CENTILE	<3rd CENTILE	48/49 (50th CENTILE)
37	KA	7	M	Nawashehar	YES	NO	YES	YES	YES	NO	YES	YES	NO	NO	NO	NO	YES	NO	UPPER MIDDLE CLASS	<3rd CENTILE	<3rd CENTILE	NA
38	NK	15	M	Moga	YES	NO	YES	YES	YES	NO	YES	NO	NO	NO	NO	NO	YES	NO	LOWER MIDDLE CLASS	10th to 25th CENTILE	10th to 25th CENTILE	NA
39	NR	4	M	Phagwara	YES	NO	YES	NO	NO	NO	YES	NO	NO	NO	NO	NO	YES	NO	LOWER MIDDLE CLASS	3rd to 50th CENTILE	3rd to 50th CENTILE	NA
40	JK	15	M	Ludhiana	YES	NO	YES	YES	YES	NO	YES	NO	NO	NO	NO	NO	YES	NO	UPPER MIDDLE CLASS	<3rd CENTILE	3rd to 10th CENTILE	NA
41	AD	10	M	Sangrur	YES	NO	YES	NO	NO	YES	YES	NO	NO	NO	NO	NO	NO	NO	LOWER MIDDLE CLASS	10th to 25th CENTILE	10th to 25th CENTILE	NA
42	NR	4	M	Ludhiana	YES	NO	YES	NO	NO	NO	YES	NO	NO	NO	NO	NO	YES	NO	LOWER MIDDLE CLASS	<3rd CENTILE	3rd to 50th CENTILE	54/50 (50th CENTILE)
43	MP	3	F	Samrala	YES	NO	YES	YES	NO	NO	YES	NO	NO	NO	NO	NO	YES	NO	UPPER MIDDLE CLASS	< 3rd CENTILE	3rd to 50th CENTILE	46/48.5 (3rd to 50th CENTILE)
44	AP	1.5	M	Khanna	YES	NO	NO	YES	YES	NO	YES	NO	NO	NO	NO	NO	YES	NO	UPPER MIDDLE CLASS	3rd CENTILE	< 3rd CENTILE	45/46.5 (3rd to 50th CENTILE)
45	GS	4.5	M	Bhatinda	YES	NO	NO	YES	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	UPPER MIDDLE CLASS	3rd to 50th CENTILE	3rd to 50th CENTILE	51 cm/50cm (50th CENTILE)
46	JS	2.5	M	Ludhiana	YES	NO	YES	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	LOWER MIDDLE CLASS	3rd to 50th CENTILE	3rd to 50 th CENTILE	49/48 (50th CENTILE)
47	GO	11	M	ludhiana	YES	YES	NO	NO	YES	NO	YES	NO	NO	NO	NO	NO	NO	NO	UPPER CLASS	10th to 25th CENTILE	25th to 50th CENTILE	NA
48	JP	10	M	Ludhiana	YES	YES	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	YES	YES	UPPER MIDDLE CLASS	3rd to 10th CENTILE	10th to 25th CENTILE	NA
49	AP	14	F	Ludhiana	YES	NO	YES	YES	YES	NO	YES	NO	NO	NO	NO	NO	YES	YES	UPPER MIDDLE CLASS	< 3rd CENTILE	10th to 25th CENTILE	NA
50	AD	12	M	Patiala	YES	NO	YES	NO	YES	NO	YES	NO	NO	NO	NO	NO	NO	NO	LOWER MIDDLE CLASS	3rd to 10th CENTILE	< 3rd CENTILE	NA
51	JD	14	M	Malaout	YES	YES	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	YES	NO	UPPER MIDDLE CLASS	10th to 25th CENTILE	25th to 50th CENTILE	NA
52	DV	7	M	Patiala	YES	YES	NO	YES	NO	NO	YES	NO	NO	NO	NO	NO	YES	NO	UPPER MIDDLE CLASS	25th to 50th CENTILE	25th to 50th CENTILE	NA
53	SD	6	M	Bathinda	YES	NO	NO	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	LOWER MIDDLE CLASS	3rd to 10th CENTILE	10th to 25th CENTILE	NA
54	GS	9	M	Ludhiana	YES	YES	NO	YES	YES	NO	YES	NO	NO	NO	NO	NO	YES	NO	UPPER MIDDLE CLASS	10th to 25th CENTILE	10th to 25th CENTILE	NA
55	IY	2.5	F	Ludhiana	YES	NO	YES	NO	NO	YES	YES	NO	NO	NO	NO	NO	NO	NO	UPPER MIDDLE CLASS	< 3rd CENTILE	3rd to 50th CENTILE	46.5/47.9 (25th to 50th CENTILE)
56	EV	3	M	Khanna	YES	YES	NO	YES	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	LOWER MIDDLE CLASS	3rd to 50th CENTILE	3rd to 50th CENTILE	48/48.5(25th to 50t h CENTILE)

	GPE													
BMI (INFERENCE)	PALLOR	RICKETS	SKIN CHANGES	NAIL CHANGES	HAEMOGRAM (Hb/TLC/Plt)	ANTI-tTG (Positive > 10)	Anti-EMA	HLADO2	HLADO8	IgA LEVEL (70-400)	MARSH GRADING	SGOT / SGPT (< 40)	VITAMIN D LEVELS (> 30: NORMAL)	ESPGHAN SCORE	DIAGNOSIS
NA	YES	NO	NO	NO	12.7/8.4/269	41.9	1+	positive	negative	53.5	0	24/17	40.9	2	COELIAC DISEASE (IgA DEFICIENCY) WITH ANAEMIA
3rd to 50th CENTILE	YES	NO	NO	NO	9.2/8.4/800	123.3	1+	positive	negative	158	0	53/22	40.5	5	COELIAC DISEASE
50th CENTILE	YES	NO	NO	NO	11.8/9.7/399	0.1	negative	positive	negative	50.1	0	29/18	32	2	COELIAC DISEASE (IgA DEFICIENCY)
NA	YES	NO	NO	YES	12.5/8.2/360	112	1+	positive	negative	161	1	21/17	21	5	COELIAC DISEASE WITH ANAEMIA
NA	YES	NO	NO	NO	12/13.1/259	158	2+	Positive	negative	162	1	24/14	12.03	5	Coeliac diseae WITH VITAMIN D DEFICIENCY
NA	YES	NO	NO	NO	10.2/9.1/518	121	3+	positive	negative	96	1	27/38	25	5	COELIAC DISEASE WITH IDDM WITH HYPOTHYROIDISM
NA	YES	NO	NO	NO	12.1/10.6/345	204.6	2+	positive	negative	170	1	27/18	26.05	5	COELIAC DISEASE WITH ANAEMIA WITH VITAMIN D DEFICIENCY
NA	YES	NO	NO	NO	11.9/6.8/294	160	4+	positive	negative	94	1	28/15	37	5	COELIAC DISEASE WITH IRON DEFICIENCY ANAEMIA
NA	YES	NO	NO	NO	12/7.1/278	212	3+	positive	negative	113	1	18/32	23	5	COELIAC DISEASE WITH IRON DEFICIENCY ANAEMIA WITH VITAMIN D DEFICIENCY
NA	YES	NO	NO	NO	8.6/6.7/259	110	2+	positive	negative	86	1	38/25	17.8	5	COELIAC DISEASE WITH IRON DEFICIENCY ANAEMIA WITH Vit D DEFICIENCY
NA	YES	NO	NO	NO	11.7/6.5/324	280	1+	positive	negative	132	2	24/48	12.9	6	COELIAC DISEASE WITH ANAEMIA WITH VITAMIN D DEFICIENCY
NA	YES	NO	YES	YES	11.6/6.6/399	168	1+	positive	negative	134	2	18/18	23	6	COELIAC DISEASE WITH DERMATITIS HERPITIFORMIS
3rd to 50th CENTILE	YES	NO	NO	YES	10.3/7.7/232	300	4+	positive	positive	146	2	29/28	22	6	COELIAC DISEASE WITH VITAMIN D DEFICIENCY WITH RHINITIS
NA	YES	NO	NO	YES	14.5/10.6/526	300	4+	positive	negative	201	2	22/19	28	6	COELIAC DISEASE WITH RHINITIS WITH ANAEMIA
NA	YES	NO	NO	YES	11.1/9.2/318	300	1+	positive	positive	138	2	31/29	27	6	COELIAC DISEASE WITH ANAEMIA
NA	YES	NO	NO	NO	11.7/12.9/380	100	2+	positive	negative	72.1	2	18/14	23.04	6	COELIAC DISEASE WITH ANAEMIA WITH VITAMIN D DEFICIENCY
NA	YES	NO	NO	NO	11.5/10.2/357	182	2+	positive	negative	136	2	29/28	29	6	COELIAC DISEASE
3rd to 50th CENTILE	YES	NO	NO	NO	11/10.4/235	101	3+	positive	negative	94	2	31/29	23.5	6	COELIAC DISEASE WITH IRON DEFICIENCY ANAEMIA WITH Vit D DEFICIENCY
NA	YES	NO	NO	NO	13.4/10.5/257	190	2+	positive	negative	206	2	19/15	16.9	6	COELIAC DISEASE WITH IRON DEFICIENCY ANAEMIA WITH VITAMIN D DEFICIENCY
3rd to 50th CENTILE	YES	NO	NO	NO	11.4/4.7/366	260	2+	positive	negative	88	2	54/44	25	6	COELIAC DISEASE WITH IRON DEFICIENCY ANAEMIA WITH Vit D DEFICIENCY
NA	YES	NO	NO	YES	10.1/8.7/204	134	1+	positive	negative	89.4	3A	24/27	23.5	6	COELIAC DISEASE WITH ANAEMIA WITH VITAMIN D DEFICIENCY
NA	YES	NO	NO	NO	8.7/7.6/590	160	4+	positive	negative	113.2	3A	19/21	17.2	6	COELIAC DISEASE WITH IRON DEFICIENCY ANAEMIA WITH VITAMIN D DEFICIENCY
50th CENTILE	YES	NO	NO	NO	10.2/11.1/447	300	2+	positive	negative	119	3A	20/18	31	7	COELIAC DISEASE
3rd to 50th CENTILE	YES	NO	NO	YES	8/6.09/266	360	2+	positive	negative	187	3A	28/31	17	6	COELIAC DISEASE WITH IRON DEFICIENCY ANAEMIA WITH Vit D DEFICIENCY WITH k/c/o ASD WITH Perimembranous VSD
50th CENTILE	YES	NO	NO	NO	9.2/7.8/375	184	2+	positive	negative	201.2	3A	24/18	31	6	COELIAC DISEASE WITH IRON DEFICIENCY ANAEMIA WITH Vit D DEFICIENCY
NA	YES	NO	NO	YES	8.3/7.6/790	300	4 +	positive	negative	196	3B	24/18	12	7	COELIAC DISEASE WITH ANAEMIA WITH VITAMIN D DEFICIENCY
NA	YES	NO	NO	YES	14.2/12.3/384	300	3+	positive	positive	159	3B	27/18	27.5	7	COELIAC DISEASE WITH ANAEMIA WITH VITAMIN D DEFICIENCY WITH ALLERGIC ASTHMA
NA	YES	NO	NO	YES	12/12.3/519	140	3+	Positive	negative	204	3B	41/17	26	7	COELIAC DISEASE WITH VITAMIN D DEFICIENCY
3rd to 50th CENTILE	YES	NO	NO	NO	9.4/7.4/421	136	4+	positive	negative	117	3B	19/15	29	7	COELIAC DISEASE WITH IRON DEFICIENCY ANAEMIA WITH VITAMIN D DEFICIENCY
NA	YES	NO	NO	YES	10.9/10.4/306	>300	2+	positive	negative	76.3	3B	20/17	26.14	7	COELIAC DISEASE WITH IRON DEFICIENCY ANAEMIA WITH VITAMIN D DEFICIENCY
NA	YES	NO	NO	YES	9.3/6.1/422	114	4+	positive	negative	158	3B	30/19	17.5	7	COELIAC DISEASE WITH IRON DEFICIENCY ANAEMIA WITH VITAMIN D DEFICIENCY
50h CENTILE	YES	YES	NO	YES	7.4/10.8/542	170	2+	positive	negative	236	3B	28/15	6.2	7	COELIAC DISEASE WITH RICKETS(VDDR) WITH ANAEMIA
NA	YES	NO	NO	NO	11.8/6.6/494	300	2+	positive	negative	190	3B	32/17	21.2	7	COELIAC DISEASE WITH IRON DEFICIENCY ANAEMIA WITH Vit D DEFICIENCY
3rd to 50th CENTILE	YES	NO	NO	NO	10.3/5.7/437	>300	2+	positive	positive	305	3B	25/19	24.5	7	COELIAC DISEASE WITH IRON DEFICIENCY ANAEMIA WITH Vit D DEFICIENCY
NA	YES	NO	NO	NO	11.2/6.9/361	300	4+	positive	negative	117	3B	69/18	15.3	7	COELIAC DISEASE WITH IRON DEFICIENCY ANAEMIA WITH Vit D DEFICIENCY
50th CENTILE	YES	NO	NO	YES	8/11.4/266	360	3+	positive	negative	280.4	3C	19/23	46	7	COELIAC DISEASE WITH ANAEMIA
NA	YES	NO	NO	YES	10.2/9.1/376	300	1+	positive	negative	257	3C	26/30	14	7	COELIAC DISEASE WITH VITAMIN D DEFICIENCY
NA	YES	NO	NO	YES	12.4/8/265	310	2+	positive	positive	294	3C	17/19	25.4	7	COELIAC DISEASE WITH ANAEMIA WITH VITAMIN D DEFICIENCY
3rd to 50th CENTILE	YES	NO	YES	NO	12/7/291	300	3+	positive	positive	298	3C	35/20	22.3	7	COELIAC DISEASE WITH ANAEMIA WITH VITAMIN D DEFICIENCY
NA	YES	NO	NO	YES	7.9/8/526	147	3+	positive	negative	297	3C	51/44	18.5	7	COELIAC DISEASE WITH ANAEMIA WITH VITAMIN D DEFICIENCY
NA	YES	NO	NO	NO	10/6.6/742	300	4+	positive	positive	214	3C	28/32	32	7	COELIAC DISEASE WITH ANAEMIA
50th CENTILE	YES	NO	YES	YES	12/5.4/358	>300	3+	positive	negative	91	3C	35/20	22.3	7	COELIAC DISEASE WITH IRON DEFICIENCY ANAEMIA WITH Vit D DEFICIENCY
3rd to 50th CENTILE	YES	NO	NO	NO	7.8/5.1/270	300	3+	positive	positive	84	3C	31/27	12.7	7	COELIAC DISEASE WITH IRON DEFICIENCY ANAEMIA WITH Vit D DEFICIENCY
3rd to 50th CENTILE	YES	NO	NO	NO	10.6/6.2/528	230	3+	positive	negative	161	3C	29/16	7.2	7	COELIAC DISEASE WITH IRON DEFICIENCY ANAEMIA WITH Vit D DEFICIENCY
50th CENTILE	YES	NO	NO	NO	10.2/10/400	200	1+	positive	negative	91.4	3A	32/21	21	5	COELIAC DISEASE WITH ANAEMIA
50th CENTILE	YES	NO	NO	NO	9.3/ 16/531	300	4 +	positive	negative	162.6	3B	28/21	14.1	5	COELIAC DISEASE
NA	YES	NO	NO	NO	12.9/12/304	160	4+			98		18/21			COELIAC DISEASE
NA	YES	NO	NO	NO	13.1/8.9/278	212	3+	positive	negative	126		32/18	23		COELIAC DISEASE WITH VITAMIN D DEFICIENCY
NA	YES	NO	NO	NO	9.6/11.9/182	160						18/20	5.06		COELIAC DISEASE WITH VITAMIN D DEFICIENCY
NA	YES	NO	NO	YES	9.4/11.8/370	160		positive	negative			29/19			COELIAC DISEASE
NA	YES	NO	NO	NO	9.3/12/225	300				134.9		27/23	19.2		COELIAC DISEASE WITH VITAMIN D DEFICIENCY
NA	YES	NO	NO	NO	9.3/6.7/301	160	4+	positive	negative			35/29	25.02		COELIAC DISEASE WITH ANAEMIA WITH VITAMIN D DEFICIENCY
NA	YES	NO	NO	YES	11/7.4/319	300	2+	positive	negative			27/21	71		COELIAC DISEASE
NA	NO	NO	NO	NO	11/10/449	106	2+			158		29/20	16.3		COELIAC DISEASE WITH ANAEMIA WITH VITAMIN D DEFICIENCY
3rd to 50th CENTILE	YES	NO	NO	NO	9.3/13.9/594	360	2+	positive	negative	150		17/41	38.5		COELIAC DISEASE
3rd to 50th CENTILE	YES	NO	NO	NO	8.6/14/259	300	2+	positive	negative	172		38/29	29.2		COELIAC DISEASE

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Subject: **Approval of Plan of Thesis.**

This is to inform you that the Faculty of Medical Sciences in its meeting held on 29.05.2019 has approved the plan of thesis of **Amita Sodhi**, a student of your college for **MD Paediatrics** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis

Diagnosis of coeliac disease in children of Punjab region as per the new espghan guidelines

Supervisor
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The student has to submit the four copies of thesis (along with PDF format) , to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

S P Singh

Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

1. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*
2. *The student may submit the thesis as per the schedule already conveyed i.e for May/June examination 30th Nov of the preceding the year of examination and for Nov/Dec examinations 31st May of the year of examination.*

DIAGNOSIS OF COELIAC DISEASE IN CHILDREN OF PUNJAB REGION AS PER THE NEW ESPGHAN GUIDELINES

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTOR OF MEDICINE

In

PEDIATRICS

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES
FARIDKOT

DECEMBER, 2018

DR. AMITA SODHI

DEPARTMENT OF PEDIATRICS
DAYANAND MEDICAL COLLEGE AND HOSPITAL
LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	DIAGNOSIS OF COELIAC DISEASE IN CHILDREN OF PUNJAB REGION AS PER THE NEW ESPGHAN GUIDELINES
For the degree of	MD (Paediatrics)
Name of the candidate	Dr. Amita Sodhi
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Introduction: Coeliac disease(CD) sometimes called as sprue or gluten sensitive enteropathy, is an immune mediated inflammatory disorder elicited by the ingestion of gluten and related prolamines in genetically susceptible individuals and characterized by the presence of a combination of gluten dependent clinical manifestations, CD-specific antibodies, HLA DQ2/DQ8 halotypes and enteropathy. Over the last two decades, the understanding of CD has changed from an uncommon enteropathy to a multi organ disease. It is no longer considered a disease of the developed world, its widespread prevalence has been well documented in studies from different developing countries. Prevalence of celiac disease is considered to be around 1% as per the recent studies.

Aim of Study: To evaluate triple test as a diagnostic criteria for coeliac disease.

Materials & Methods: This is a prospective observational study being conducted in the paediatric age group of the Punjab region aged between 1 year to 18 years, coming to the Department of Paediatrics at Dayanand Medical College & Hospital, Ludhiana. The duration of the study is going to be 1 ½ year.

Clinical Significance: This study will be helpful in omitting the need for an invasive procedure(i.e.biospy) in children, reduces the diagnostic time and will also be cost effective in diagnosis of coeliac disease in future.

Keywords: Coeliac disease, ESPGHAN guidelines, serological marker, Anti-tTG, anti-EMA, HLA-DQ, diagnosis.

(Signature)	(Signature)	(Signature)	(Signature)	(Signature)
Candidate	Co-supervisor	Co-supervisor	Supervisor	Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis entitled **"DIAGNOSIS OF COELIAC DISEASE IN CHILDREN OF PUNJAB REGION AS PER THE NEW ESPGHAN GUIDELINES."** exist in the Department of Pediatrics, Dayanand Medical College and Hospital, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis are genuine and is collected by the candidate herself under our supervision and guidance.

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5	TITLE OF THE TOPIC	DIAGNOSIS OF COELIAC DISEASE IN CHILDREN of PUNJAB REGION AS PER THE NEW ESPGHAN GUIDELINES

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Guidelines from the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) for the diagnosis and treatment of coeliac disease (CD) have not been renewed for 20 years. The perception of CD has now changed from an uncommon enteropathy to a common multiorgan disease. The diagnosis of CD also has changed as a result of the availability of CD-specific antibody tests. Within ESPGHAN, a working group was established to formulate new guidelines for the diagnosis of CD based on scientific and technical developments using an evidence-based approach.[1]

CD is an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals and characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies.

The diagnostic criteria for coeliac disease in children were first established in 1969. It stated the 3-biopsy rule: i.e. to perform at least 3 small bowel biopsy(SBB), characteristic histological lesions in first SBB led to diagnosis of suspected Coeliac disease, but only after confirmation of histological relapse in third biopsy related to gluten challenge(GC), a definitive diagnosis of CD could be confirmed. These rules were followed for 20 years.[2]

This diagnostic criterion was modified in 1990. The GC was now restricted to infants younger than 2 years at the first biopsy to exclude other causes of enteropathy. Under this criterion, presence of CD anti gliadin antibodies (AGA) at the onset of disease was taken into account, followed by antibody vanishing after gluten withdrawal, added support to the diagnosis.[3]

Eventually development of anti endomysial antibodies(EMA) in 1980,with tissue transglutaminase antibodies (tTG) being recognized as the auto-antigen to CD led to identification of autoimmune nature of coeliac disease in 1990, represented a true revolution in the field of celiac disease. These antibodies (EMA & tTG) have been observed to show a sensitivity and specificity of > 95%. A strong association of CD with the genetic markers Human Leukocyte Antigen(HLA)-DQ2 and/or DQ8, which when combined reach a sensitivity of >96% in most populations has been established.[2] Lately, critical voices have been claiming that in view of their higher diagnostic accuracy, specific antibody testing may replace the SBB in diagnosis.[4]

The ESPGHAN has revised the approach for diagnosis of CD in 2012. A new definition of coeliac disease proposed: is a chronic disease with multi-organ involvement, immune-mediated systemic disorder, gluten dependent clinical manifestations, related to anti-tissue transglutaminase antibodies (Anti-tTG), with small intestinal inflammation.[2]According to it, the diagnosis of coeliac disease cannot rely on one single parameter, but on combination of clinical symptoms, CD-specific autoantibodies, histology and genetics. A scoring system has been proposed but has to be formally evaluated in prospective clinical studies before it can be recommended in regular clinical use.[1]

The implications of change of criteria will present a better outlook since there is omission of biopsy in selected cases as per these ESPGHAN guidelines.

There are some retrospective studies done but there is paucity of application of these latest guidelines in clinical scenarios in India. In our study we want to assess the application of these latest ESPGHAN guidelines in children of our region.

6.2 REVIEW OF LITERATURE

Upper endoscopy is a common procedure performed by gastroenterologists to investigate dyspepsia, dysphagia and other upper gastrointestinal symptoms. This offers an opportunity to obtain duodenal biopsies to establish or exclude the diagnosis of celiac disease.

Coeliac disease is increasingly detected using immunoglobulin A antitissue transglutaminase antibody serology, which has operating characteristics perfectly suited for a screening test. Whether a biopsy is still required to confirm the diagnosis is debated, but in clinical practice, an endoscopy and biopsy is often performed to confirm the diagnosis. The serological titres are then often followed-up to assess adherence to gluten-free diet and adequate resolution of coeliac disease by diet [5] However, this approach requires considerable investment of time and resources by pathologists.

The diagnosis of coeliac disease requires a specific histopathological assessment. The mucosal architecture is the cornerstone of the histological classifications. Different confounding disorders should be considered in the differential diagnosis with coeliac disease. Dysbiosis could play a role in the activation of the immune system leading to the development of coeliac disease.[6]

Despite the knowledge of clinical, serological and histological typical lesions, there are some conditions to consider for differential diagnosis. From the first description of histology of CD, several studies were conducted to define similar findings suggestive for microscopic enteritis. Considering the establishment of early precursor lesions, the imbalance of gut microbiota is another point still requiring a detailed definition.

Freeman[7] reported a long experience of diagnosing coeliac disease using duodenal biopsies during upper endoscopy and the resultant increased diagnosis of coeliac disease in the population.

Duodenal bulb biopsies may increase diagnostic yield because villous atrophy may be patchy.[8]

A recent study has shown that modern high-definition endoscopic techniques with image enhancement may be accurate in diagnosing villous atrophy.[9] It may, therefore, be possible to only perform confirmatory duodenal biopsies, two from the duodenal bulb and four to six from the distal duodenum, where villous atrophy is suspected at high-definition endoscopy, with image enhancement techniques built into modern endoscopes.

Marsh modified type 1 histology grade may, of course, miss recognition by endoscopic techniques. Endoscopic and histological demonstration of villous atrophy alone needs to be distinguished from causes other than coeliac disease. So the duodenal biopsy is the gold standard for the diagnosis of coeliac disease. However, given improvements in the performance of serological testing, the possibility of accurately diagnosing coeliac disease without the need of a biopsy has attracted interest.

The 2012 European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guideline for diagnosis of celiac disease (CD) questioned the need for intestinal biopsy to confirm the diagnosis. The guideline recommends that in symptomatic patients with consistent human leukocyte antigen (HLA) subtypes, the diagnostic accuracy of strongly positive serology is sufficient to confirm the diagnosis.

The European Society for Paediatric Gastroenterology, Hepatology and Nutrition has revised its recommendations to include a diagnostic algorithm that includes sequential serological testing and HLA genotyping for symptomatic children which would enable a diagnosis of coeliac disease to be made in the absence of a confirmatory intestinal biopsy.

Recent studies have evaluated the ESPGHAN guidelines and have mostly corroborated that coeliac disease can be accurately diagnosed in specific pediatric patient populations without the need of a biopsy. However, two cautionary points have been raised that warrant further consideration – the success of this approach is highly dependent targeting a population with a high pretest probability of celiac disease, as well, the performance of serology assays must be established and the appropriate use of cutoffs is essential.

The main conclusions of these guidelines are that the diagnosis of CD depends on gluten-dependent symptoms, CD-specific antibody levels, the presence of HLA-DQ2and/or HLA-DQ8, and characteristic histological changes (villous atrophy and crypt hyperplasia) in the duodenal biopsy. High TG2-antibody levels (10 times ULN for a standard curve-based calculation) as measured by a qualified laboratory show high diagnostic accuracies. In the presence of high antibody levels the diagnosis of CD may be based on a combination of symptoms, antibodies, and HLA, thus omitting the duodenal biopsy. The diagnosis is confirmed by an antibody decline and preferably a clinical response to a GFD. Gluten challenge and repetitive biopsies will be necessary only in selected patients in whom diagnostic uncertainty remains. The present guidelines replace the existing ESPGHAN guidelines, but require a period of implementation and testing.[10] It will be important to be precise in

the clinical evaluation of patients and to perform prospective research studies. Likewise, it will be important for laboratories performing analyses of CD antibodies and HLA determinations to develop methodologies and continuously participate in quality control programmes. Based on the current evidence symptoms, CD-specific antibodies, HLA, and biopsy findings contribute to the CD diagnosis. A wide spectrum of findings is present within each item, from suggestive to contradictory. For example, a malabsorption syndrome is more convincing than alopecia or being a person belonging to a risk group. Likewise, histological lesions with severe villous atrophy (Marsh 3b and 3c) are more convincing than Marsh 1 lesions. In the hierarchy of antibodies, EMA has the highest impact, whereas negativity for all antibodies on an unrestricted diet or absence of both HLA-DQ2 and HLA-DQ8 strongly contradict the presence of CD.

Nonetheless, an unconventional HLA-DQ type cannot totally exclude CD, and typical gluten-responsive lesions can be present even in the absence of CD antibodies in serum. A scoring system may be applied so that a stronger finding in one item may compensate for a missing abnormality in another and the sum could be taken into account. The main function of a scoring approach is to assist in interpretation of diagnostic findings and to protect against over diagnosis. Such scoring systems must be evaluated formally in prospective study.

S. Hubsy et al. [1] for the ESPGHAN working group on coeliac disease diagnosis on behalf of the ESPGHAN Gastroenterology committee made a panel of 17 experts & defined Coeliac disease and developed new diagnostic criteria based on the Delphi process. Two groups of patients were defined as

children with symptoms suggestive of CD in group 1 and asymptomatic children at increased risk for CD in group 2. In group 1, the diagnosis of CD is based on symptoms, positive serology, and histology that is consistent with CD. If IgA anti-tissue transglutaminase type 2 antibody titres are high >10 times the upper limit of normal, then the option is to diagnose CD without duodenal biopsies by applying a strict protocol with further lab tests. In group 2, the diagnosis of CD is based on positive serology, and histology. HLA DQ2 & DQ8 testing is valuable because CD is unlikely if both halotypes are negative.

Gabriela Klapp et al.[11] wrote an abstract on application of ESPGHAN guidelines where they did a retrospective review of all patients suspected of having CD who had undergone a small bowel biopsy. All symptomatic children with serological markers positive were included in the study. Out of them, 116 were positive for the triple test serological markers positive, 113 of 116 had a Marsh 2/3 histological lesion and had been considered to have CD. Thus positive predictive value of triple test was 97.4%. The other 3 cases (2.6 %) had Marsh 0/1 lesion, so we consider them to be false positive for TT, however on follow up, all 3 children developed histological damage after a gluten challenge test. Finally the positive predictive test for triple test was 100%. The authors commented that in low resource countries, these guidelines were applicable in symptomatic children with TT positivity and a diagnosis of coeliac could be easily established in them.

P.G. Hill et al.[12] did a study where he said that in view of high diagnostic accuracy of Immunoglobulin, a tissue transglutaminase antibodies for detecting coeliac disease, a small biopsy is not always needed. The anti –tTG

antibody gives a positive predictive value of 100%. They also commented that biopsies showing mild histopathological lesions are difficult to interpret. They had used the cut off >10times the upper limit of anti-tTg. As per them 58% of 112 new diagnoses had levels above this cut off and biopsy was not needed in them.

Jonathan Bishop et al.[13] concluded in a prospective study that the ESPGHAN guideline performs well in New Zealand Children population. Adoption of the guideline would reduce the number of patients requiring endoscopy without compromise in diagnostic accuracy. In this study histological findings according to Marsh criteria were correlated with blood results and the accuracy of the guideline was analyzed. The study also examined the role of deamidated gliadin peptide (DGP) in the diagnosis of CD. For symptomatic patients with consistent HLA subtypes, strongly positive serology (as described in the ESPGHAN guidelines) accurately predicted biopsy-proven CD in >95% of cases. DGP was positive in fewer patients than anti-TG2 or EMA. Incorporation of DGP as a second confirmatory serological test in place of EMA was associated with maintained predictive value of guideline, but fewer patients fulfilling criteria for biopsy-free diagnosis. The involvement of pediatric gastroenterological expertise, however, remains key to diagnosis of CD.

Summary: The duodenal biopsy will remain the gold standard for diagnosing celiac disease in a majority of patients. However, as serology assays evolve and as a greater understanding of the genetic risk factors of celiac disease is achieved, more patients may be accurately diagnosed without the need for a biopsy.[14]

6.3 AIMS AND OBJECTIVES

To evaluate triple test as a diagnostic criteria for coeliac disease.

7. MATERIALS AND METHODS

7.1 SOURCE OF DATA

Children of age group 1 year to 18 years coming to the OPD & IPD of Department of Paediatrics at DMC&H, Ludhiana.

7.2 METHOD OF COLLECTION OF DATA

This is a prospective observational study being conducted in the paediatric age group of the Punjab region aged between 1 year to 18 years of age coming to the Department of Paediatrics at Dayanand Medical college & Hospital, Ludhiana. The duration of the study is going to be 1 ½ year.

INCLUSION CRITERIA

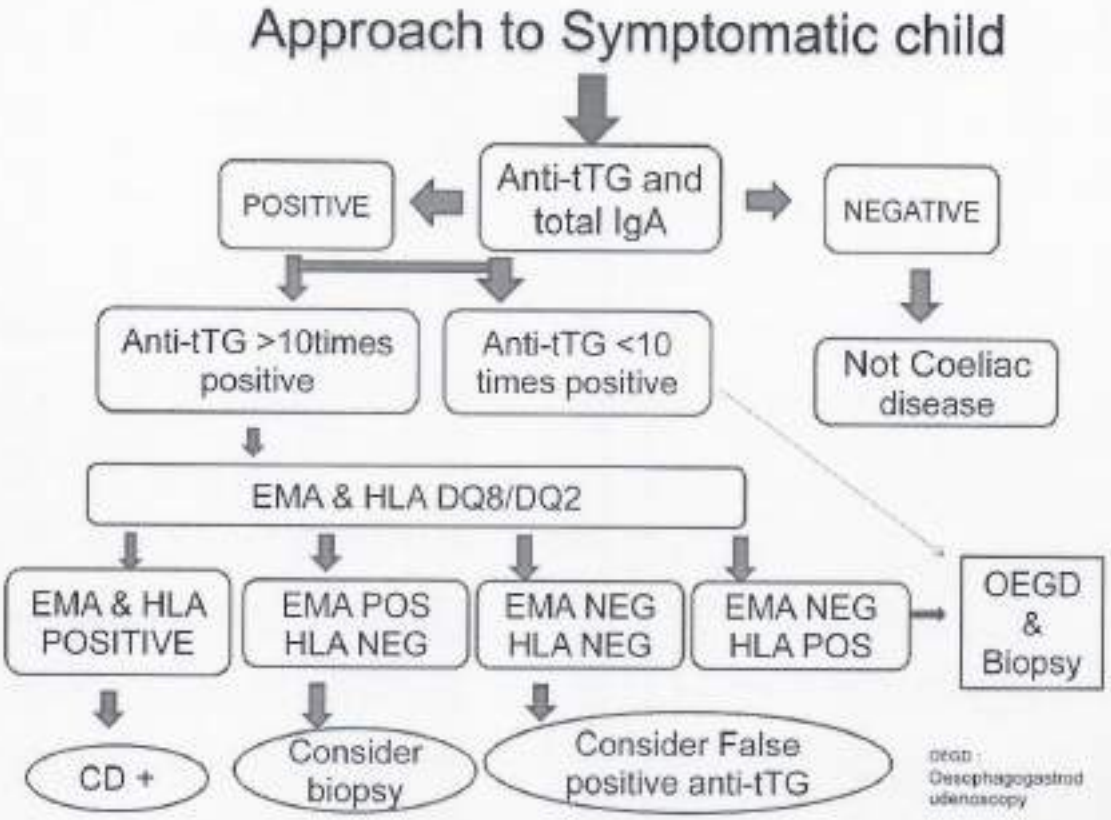
- Children from 1 year to 18 years of age.
- All children coming in OPD & IPD will be included
- Informed consent to be taken
- Clinically Children with symptoms suggestive of coeliac disease
- Serological marker positivity of Triple test (Anti-tTG, EMA & HLA-DQ2,DQ8)

EXCLUSION CRITERIA

- Children below 1 year of age.
- Patient or parents not giving consent for the study
- Serological Markers negative

Methodology

Diagnosis of coeliac disease will be based on revised ESPGHAN criteria. Study will include children between 1year to 18 years, presenting with symptoms suggestive of coeliac disease. Triple test and biopsy will be done to diagnose coeliac disease.



STUDY TYPE: Prospective Observational Study

DURATION OF STUDY: 1 ½ Year

OUTCOME: This study will assess the new ESPGHAN guidelines and their use in diagnosis of coeliac disease with less need of biopsy in serology positive patient.

STATISTICAL ANALYSIS

Data will be described in terms of range; mean ±standard deviation (± SD), frequencies (number of cases) and relative frequencies (percentages) as appropriate. All statistical calculations will done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY

It requires only routine investigations, serological markers investigations and biopsy.

7.4 HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF?

Yes, attached along with.

8. LIST OF REFERENCES

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4. Barker CC, Mitton C, Jevon G, Mock T. Can tissue transglutaminase antibody titres replace small bowel biopsy to diagnose celiac disease in selected pediatric populations? Pediatrics. 2005;115:1341-6.
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10. Paul SP, Mazhar H, Spray CH. Applicability of the New ESPGHAN Guidelines for Diagnosing Coeliac Disease in Children from Resource Limited Countries. Journal of the College of Physicians and Surgeons Pakistan. 2015;25(6):455-7
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12. Hill PG, Holmes GK. Coeliac disease: a biopsy is not always necessary for diagnosis. Aliment Pharmacol Ther. 2008;27(7):572-7.
13. Bishop J, Reed P, Austin P, Hurst M, Ameratunga R, Craigie A. Prospective Evaluation of the ESPGHAN Guidelines for Diagnosis of Celiac Disease in New Zealand Children. J Pediatr Gastroenterol Nutr. 2018;67(6):749-754.
14. Mills JR, Murray JA. Contemporary celiac disease diagnosis: is a biopsy avoidable? Curr Opin Gastroenterol. 2016;32(2):80-5.

PROFORMA

S. No :

Name: Age :

Father's Name : Sex :

Address : Mob.No:

MRD NO :

Chief Complaints:

Presenting Symptoms :

- Diarrhoea (yes/no) :

  No. Of stools per day:

  Consistency (watery or bulky) :

  Any foul smelling stools :

  Any blood or mucus :
- Growth failure/Short Stature
- Delayed puberty
- Anaemia
- Nausea
- Vomiting
- Abdominal Pain
- Cramping or Distension
- Constipation
- Fatigue
- Recurrent Aphthous, stomatitis(mouth ulcers)
- Dermatitis Herpetiformis – like rash
- Any allergic disorders (asthma, urticaria, rhinitis):

Signature of Candidate **Signature of Supervisor**

Any Assosciated Conditions (Yes/No)

- Type 1 Diabetes Mellitus
- Genetic d/o (Down Syndrome/Turner Syndrome)
- Thyroid disease
- William syndrome
- IgA deficiency
- Autoimune liver disease
- Any other autoimmune disease

Family History

- Any family history of celiac disease (y/n) :
- Any food allergy (Y/N) :
- Any other allergy (Y/N):
- Any history of autoimmune disease :
- Any other relevant history :

Socio Economic Status (As per modified Kuppuswamy Scale)

- Upper class
- Upper middle class
- Lower middle class
- Upper Lower class
- Lower class

Signature of Candidate **Signature of Supervisor**

Anthropometry

	Actual	Expected	Inference
Weight			
Height			
BMI			
HC			

General Physical Examination

- Pallor
- Cyanosis
- Jaundice
- Edema
- Lymphadenopathy
- Nail abnormality

  (clubbing/koilonychias/discolouration etc..)
- Cheilosis
- Rickets
- Any other Vitamin deficiency
- Skin Changes
- Hair changes
- Muscle wasting
- Any organomegaly
- Any Peripheral Neuropathy

Signature of Candidate **Signature of Supervisor**

Investigations

S.No.	Investigation	Findings
1.	Hemogram	
2.	PBF	
3.	Thyroid profile SGOT/SGPT Vit D levels	
5.	Anti-tTG (IgA)	
6.	Anti-EMA	
5.	HLA-DQ2/DQ8	
6.	IgA Levels Anti DGP	
7.	Histology as per Modified Marsh Grade	

Signature of Candidate **Signature of Supervisor**

INFORMED PATIENT CONSENT

Date: _____

I.....D/o or S/o.....

.....am willing to participate in the study **"DIAGNOSIS OF COELIAC DISEASE IN CHILDREN OF PUNJAB REGION AS PER THE NEW ESPGHAN GUIDELINES"** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

....

Signature of the Witness Signature of the patient

Name:

Signature of Supervisor **Signature of Candidate**

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य **"DIAGNOSIS OF COELIAC DISEASE IN CHILDREN OF PUNJAB REGION AS PER THE NEW ESPGHAN GUIDELINES"** में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____ _____

गवाह के हस्ताक्षर रोगी के हस्ताक्षर/अंगूठे का निशान

नाम: नाम:

_____

अन्वेषक के हस्ताक्षर

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫ਼ਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

"DIAGNOSIS OF COELIAC DISEASE IN CHILDREN OF PUNJAB REGION AS PER THE NEW ESPGHAN GUIDELINES" ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੈਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

_____
ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____

ਪਤਾ _____

_____
ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____

ਪਤਾ _____

_____
ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

_____
ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ

Scoring System as per the ESPGHAN

	Points
Symptoms	
Malabsorption syndrome	2
Other CD-relevant symptom or having T1DM or being a first-degree family member	1
Asymptomatic	0
Serum antibodies[a]	
EMA positivity and/or high positivity (>10 ULN) for anti-TG2	2
Low positivity for anti-TG2 antibodies or isolated anti-DGP positivity	1
Serological assessment not performed	0
Serological assessment performed but negative for all celiac-specific antibodies[a]	−1
HLA	
Full HLA-DQ2 (in *cis or trans*) or HLA-DQ8 heterodimers present	1
No HLA performed or half DQ2 (only HLA-DQB1*0202) present	0
HLA neither DQ2 nor DQ8 was present	−1
Histology	
Marsh 3b or 3c (subtotal villous atrophy, flat lesion)	2
Marsh 2 or 3a (moderately decreased villous height/crypt depth ratio) or marsh 0–1 plus intestinal TG2 antibodies	1
Marsh 0–1 or no biopsy performed	0

CD, celiac disease.
[a]IgG deficiency to IgG class EMA, TG2, and DGP antibodies.

Score of the patient as per the scoring system:

Diagnosis:

Signature of Candidate **Signature of Supervisor**